VOLUME 80 NUMBER 3

# AMERICAN JOURNAL

OF

# DISEASES OF CHILDREN

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## SPECIAL NOTICE

Beginning with the October 1950 issue, it is planned to introduce several changes in the covers of all the A. M. A. specialty journals.

The cover of this journal will be white enamel stock with title identification as the A. M. A. American Journal of Diseases of Children in color, with date, volume and number also in color. The Table of Contents, which is now carried on the back cover, will be placed in the front of the journal directly preceding the lead article or editorial. Second, third and fourth covers will be used for color advertising.

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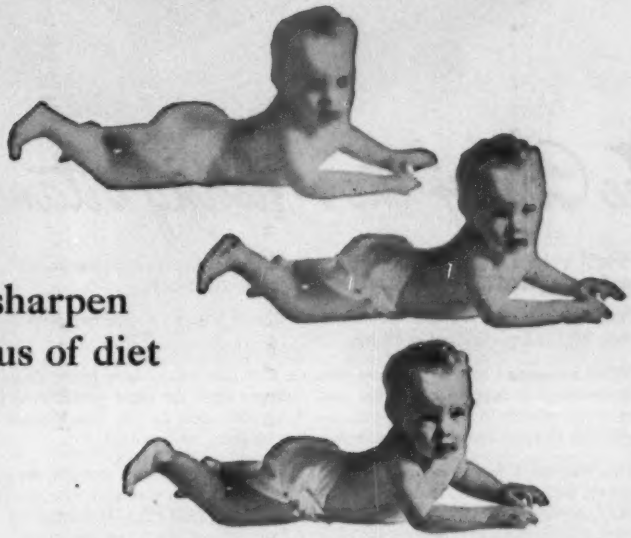

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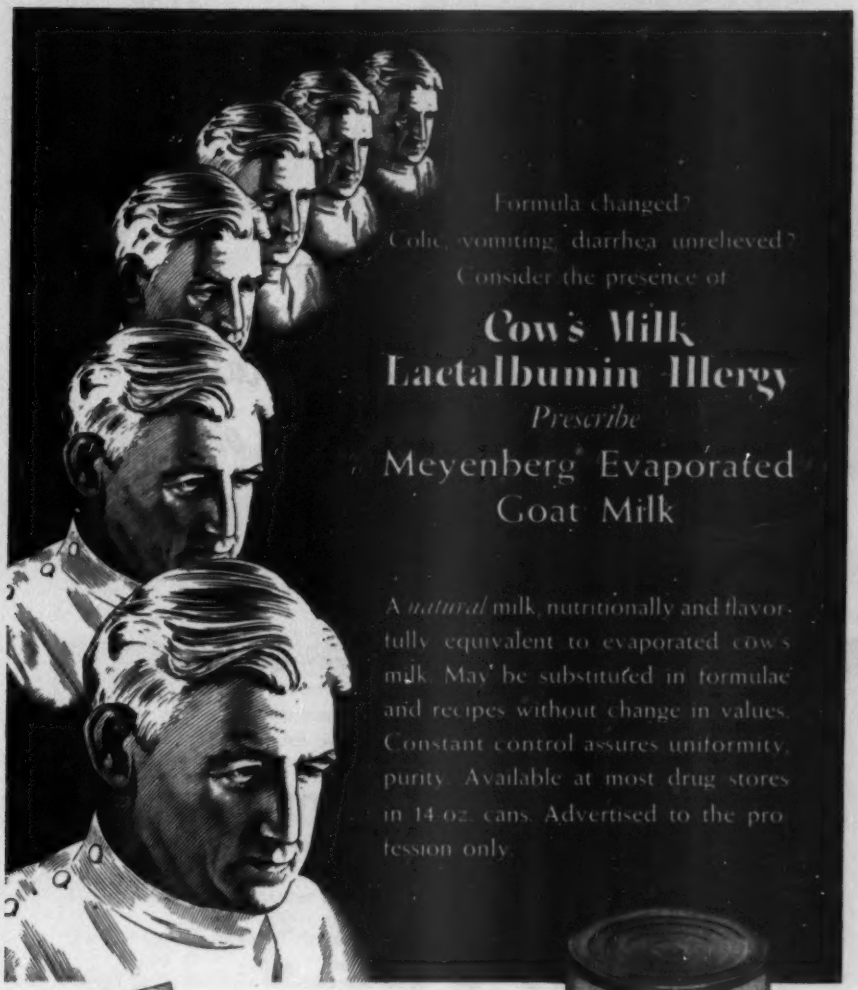

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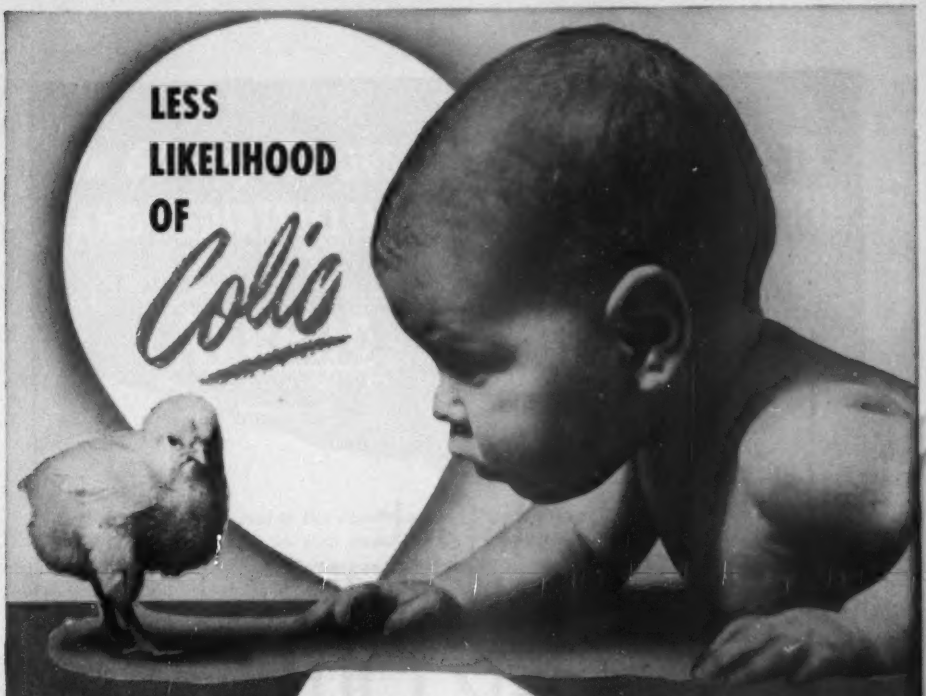

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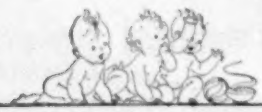

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[1]Cooke, R. A.: *Allergy in Theory and Practice*, Philadelphia: W. B. Saunders Company, 1947, p. 180

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American Journal of Diseases of Children

VOLUME 80 SEPTEMBER 1950 NUMBER 3

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# APPLICATION OF NUTRITION RESEARCH TO EVERYDAY PRACTICE

PHILIP C. JEANS, M.D.
IOWA CITY

KNOWLEDGE of nutrition has made tremendous advances in the last generation, possibly more than in all time preceding. It is still increasing and at an accelerated rate. Several thousand research workers are now engaged in investigations of food and nutrition in this country alone. These studies are being carried out in many centers through personal initiative and fostered by universities, foundations and governmental and commercial agencies. Much of the research is of fundamental character, and its immediate practical application is not always clear. Research of the basic type is essential. Through it we gain knowledge of life processes. A gap between fundamental research and its practical application and a lag in its application are to be expected. Sometimes this lag is long. Approximately thirty years ago Hamilton [1] pointed out that prematurely born babies could not have good bone mineralization while receiving human milk alone. It was not until about ten years ago that this observation had general practical application. Perhaps we can prophesy a similar lag in the application of the newly determined requirement of the prematurely born baby for vitamin D. Despite these and other lags of application, we can expect a steady development of practical measures based on the results of nutrition research, fundamental or otherwise.

Life expectancy is increasing. This increase has been accomplished through many factors, including control of sanitation, immunizations, use of antibiotics and new drugs and better nutrition. Of these various factors, the greatest progress in research at present is being made in nutrition. Only recently has it been possible to use reasonably adequate knowledge of nutritional requirements as a basis for prescribing amounts of nutrients that assure good nutrition. Much of the current knowledge in this field is summarized in the Recommended Dietary

From the Department of Pediatrics, College of Medicine, State University of Iowa.

Presidential address read at the Fifty-First Annual Meeting of the American Pediatric Society, French Lick, Ind., May 9, 1950.

1. Hamilton, B.: The Calcium and Phosphorus Metabolism of Prematures, Acta pædiat. **2**:1, 1923.

Allowances of the National Research Council,[2] a publication that represents practical application of a large amount of nutrition research.

Many discoveries may be classed as new. Important new vitamins have been identified recently, and it is certain that more are to come. Only recently has the adult requirement for individual amino acids been stated quantitatively; the requirement is not yet known for the growth period. The interdependence of many nutrients has been shown. The choline requirement depends on the intake of methionine and cystine, and vice versa; also the choline requirement is affected favorably by vitamin $B_{12}$ and pteroylglutamic (folic) acid. Nicotinic acid and tryptophane have reciprocal relationships, and tryptophane depends on pyridoxine for utilization. Sherman [3] has shown that in rats increased protein produces more rapid growth with a shortened life span; this injury is corrected by an increased calcium intake. We know that protein is as important as iron in the correction of some of the anemias and that protein is as important as mineral in bone growth. Vitamin $B_{12}$ is best known for its hemopoietic properties, but also it is an important growth factor. Vitamin $B_{12}$, folic acid and ascorbic acid are interrelated in producing utilization of tyrosine and phenylalanine. Our newer knowledge includes a better understanding of the functions of minerals, vitamins and amino acids and an increased knowledge of the relation of food to health. There is scarcely a nutritional essential which has not had research that has pediatric application. It is clear that other discoveries are imminent. For example, general availability of fat emulsions for use in parenteral feeding is just around the corner.

That nutrition research has had an important effect on pediatric practice is evident in many ways. One long term trend is the more rapid growth of infants and children. Body length is significantly greater now than it was thirty years ago, and it has become necessary to change our concept of normal growth. Rickets, scurvy and nutritional anemia, once so common, are now almost rare. Babies with marasmus formerly were common in our hospital wards, but now they are exceptionally rare. The mortality rate among prematurely born babies has been significantly reduced.

These and other improvements are attributable to changed concepts as to what constitutes an adequate diet for infants and children. One can list many contrasts in the past fifty years. Vitamin C was unknown thirty-five years ago, and the feeding of orange juice to babies was not routine until some years later. A similar statement may be made for vitamin D. We now recognize that iron or iron-containing foods are

2. Recommended Dietary Allowances, Reprint and Circular Series, no. 129, National Research Council, Washington, D. C., 1948.

3. Sherman, H. C.: Calcium and Phosphorus in Foods and Nutrition, New York, Columbia University Press, 1947, chap. 3.

necessary additions to the diet in early infancy and that the thiamine intake of young babies is borderline until thiamine containing-foods are added. Babies are now fed much more abundantly than formerly.

In a few ways prevalent pediatric practice in the feeding of infants does not fully conform to current knowledge of nutritional requirements, although practice is improving in these respects. Nutritional need for vitamins C and D exists at birth. The breast-fed baby is likely to receive his quota of vitamin C, but he still has an early need for vitamin D. Too often administration of vitamin D and in the case of artificially fed babies of vitamin C is delayed, even into the second month, and when administration is started the amount of vitamin C may be too small and the amount of vitamin D may soon become excessive. Often the initial amount of orange juice supplies as little as 2 to 4 mg. of ascorbic acid daily, whereas the need approximates 15 mg. Maximum calcium and phosphorus retentions are obtained with 300 to 400 units of vitamin D daily.[4] Not only are retentions no greater with any larger amount, but with the use of 1,800 units or more daily for several months appetite is decreased and as a consequence total retentions of calcium and phosphorus are decreased and linear growth is slowed.[5]

Our knowledge of the physiology and metabolism of prematurely born infants and young infants is increasing. This knowledge already has resulted in some change in pediatric practice, and it may be expected to result in further change. For some time we have known of the relatively low fat tolerance of the baby born prematurely; this knowledge causes us to give special thought to the fat-soluble vitamins. The urine of prematurely born and young infants is concentrated with difficulty, resulting in the excretion of dilute urine and a need for relatively larger amounts of fluid. Prematurely born babies have a relatively large amount of labile water, and they dehydrate quickly, often from slight causes; also they overhydrate easily with parenteral administration of fluid. Oxidation processes are defective; these babies excrete organic acids and are easily subject to acidosis if organic acids are fed, as with acidified milk. Tyrosine and phenylalanine are utilized poorly; this defect is overcome by adequate amounts of ascorbic acid,[6] as it is

4. Jeans, P. C., and Stearns, G.: The Human Requirement of Vitamin D, J. A. M. A. **111**:703 (Aug. 20) 1938. Stearns, G.; Jeans, P. C., and Vandecar, V.: The Effect of Vitamin D on Linear Growth in Infancy, J. Pediat. **9**:1 (July) 1936.

5. Jeans, P. C., and Stearns, G.: The Effect of Vitamin D on Linear Growth in Infancy: The Effects of Intakes Above 1800 U. S. P. Units Daily, J. Pediat. **13**:730 (Nov.) 1938.

6. Levine, S. Z.; Gordon, H. H., and Marples, E.: A Defect in the Metabolism of Tyrosin and Phenylalanine in Premature Infants: II. Spontaneous Occurrence and Eradication by Vitamin C, J. Clin. Investigation **20**:209 (March) 1941.

also by folic acid; thus the special need of the prematurely born baby for vitamin C is emphasized.

Because of the special susceptibility of the prematurely born baby to rickets, it has long been customary to give large amounts of vitamin D in prophylaxis. It has long appeared logical that the prematurely born baby requires no more vitamin D than does the baby born at term, but now this concept has been proved.[7] The special susceptibility to rickets exists because of the small amount of mineralization of bone at birth, the need for rapid growth and rapid mineralization and the often too small intake of calcium and phosphorus. Human milk cannot be ingested by the prematurely born baby in amounts sufficient to produce the required calcium and phosphorus retentions; for good retention human milk must be fortified. Increased vitamin D does not compensate for the low mineral intake.

The possibility of danger to the newly born baby from an excess of cow's milk has recently been pointed out[8]; the presence of relatively larger amounts of phosphorus in cow's milk in relation to the calcium content, failure of the kidneys to excrete the larger amount of phosphorus and accumulation of phosphorus in the plasma, with resulting decrease in calcium content, are all factors that may lead to tetany of the newborn; this mechanism often is associated with temporary functional hypoparathyroidism.

Retrolental fibroplasia is another newly described condition to which the prematurely born baby is subject. The cause has not been determined, but the possibility exits that it may be related to nutritional factors. The condition appeared concurrently with the use of water-miscible vitamins; this use is increasing, as is also the incidence of the disease. Owens and Owens[9] have indicated that the condition may be largely prevented by giving vitamin E in amounts well above any probable physiologic need. Kinsey and Zacharias[10] found a positive correlation between the occurrence of retrolental fibroplasia and the ingestion of water-miscible vitamins and iron; the amounts of the vitamins given were excessive and far higher than any known physiologic need. It is possible also that the dispersing agent used in the vitamin mixtures is responsible; some suggestion exists that some

7. Glaser, K.; Parmelee, A. H., and Hoffman, W. S.: Comparative Efficacy of Vitamin D Preparations in Prophylactic Treatment of Premature Infants, Am. J. Dis. Child. **77**:1 (Jan.) 1949.

8. Gardner, L. I.; Maclachlan, E. A.; Pick, W.; Terry, M. L., and Butler, A. M.: Etiologic Factors in Tetany of Newly Born Infants, Pediatrics **5**:228 (Feb.) 1950.

9. Owens, W. C., and Owens, E. U.: Retrolental Fibroplasia in Premature Infants, Am. J. Ophth. **32**:1631 (Dec.) 1949.

10. Kinsey, V. E., and Zacharias, L.: Retrolental Fibroplasia, J. A. M. A. **139**:572 (Feb. 26) 1949.

of these agents are detrimental to babies even in the small amounts used. Whatever the cause of retrolental fibroplasia, identification of the causative factors is needed promptly. In the meantime more moderate use of vitamins for prematurely born babies is indicated.

Another factor that affects the health and welfare of babies is the diet of the mothers during pregnancy. Numerous studies of the effect of maternal diet during pregnancy have been reported. It has been found that good nutrition of the mother makes child bearing less hazardous for both the mother and the baby; it reduces the complications of pregnancy and tends to assure the health of the infant. Thus a good diet for the mother is important for the well-being of both the mother and the baby. Poor maternal diet is associated with an increase in the complications of pregnancy and an increase in miscarriages, stillbirths, premature births and early deaths of infants. After birth the incidence of illness is greater than among babies of mothers who had better diets. When the maternal diet is good, the infants are heavier and longer at birth and subsequently; when the diet is poor, the babies generally are still in an inferior condition at 6 months. It has been observed that if the protein of the maternal diet is ample, the diet is likely to be adequate in all other respects. The very common inadequacy of protein and calcium during pregnancy points to the special need for milk in the diet.

A good maternal diet has still other beneficial effects on the offspring. It has been shown experimentally in rats, hamsters and primates that good nutrition during pregnancy and lactation favors in the offspring the development of teeth that are resistant to decay.[11] The same type of benefit has been shown clinically in children in the Scandinavian countries during the recent war periods. Toverud [12] found 50 per cent reduction in dental caries in the children of Norway coincident with improvement in food quality resulting from restriction of sugar imports. Because the improvement progressively increased over the years after sugar restriction, it appears that decreased ingestion of sugar in relation to oral environment was not the primary beneficial factor. Sognnaes [13] has presented similar data for European children. We have sugar, Lactobacillus acidophilus, fluorine, vitamin D and calcium and phosphorus all vying for a place in the list of factors to be considered in

11. Sognnaes, R. F.: Caries-Conducive Effect of a Purified Diet When Fed to Rodents During Tooth Development, J. Am. Dent. A. **37**:676 (Dec.) 1948.

12. Toverud, G.: Dental Caries in Norwegian Children During and After the Last World War: A Preliminary Report, Proc. Roy. Soc. Med. **42**:249 (April) 1949; Influence of General Health Supervision on the Frequency of Dental Caries in Groups of Norwegian Children, Brit. Dent. J. **86**:191 (April 14) 1949.

13. Sognnaes, R. F.: Analysis of Wartime Reduction of Dental Caries in European Children, Am. J. Dis. Child. **75**:792 (June) 1949.

relation to tooth decay. The benefit of good maternal diet gives us an additional factor for consideration. Each new fact is helpful in solving the various problems of this scourge of the human race.

One of the most widespread practical applications of nutrition research is enrichment of flour, bread, corn meal and rice. Bread enrichment is now legally mandatory in twenty-six states and two territories. Other states gradually are being added to the list. Even in those states that have no legal requirement, enriched flour and bread are generally used. This procedure represents a mass improvement in nutrition of the people of this country. A recent dietary survey [14] among pregnant women in a midwest state without a legal requirement for enrichment showed on the basis of calculated intakes that all the women appeared to receive an adequate amount of thiamine; at the lower economic levels the adequacy of thiamine was due in a very large measure to the use of enriched bread.

It often happens—in fact, it usually happens—that a nutritional discovery, instead of solving a problem, opens the way for further research and new discoveries. At the moment I have in mind the finding that casein and lactalbumin are of equal value in human nutrition as regards nitrogen balance. The long-standing concept that lactalbumin is superior to casein is based on observations with animals. Animals with fur and hair require more cystine than is easily supplied by casein. Human beings do not have this requirement. Adults have been kept in nitrogen balance with equivalent amounts of lactalbumin and casein.[15] Babies have been shown to have equal growth rates and nitrogen retentions with these two proteins.[16] Thus it appears that the protein of human milk is not superior to that of cow's milk, contrary to the concept we have held for so long and on which we have based feeding practices. The basis of the conceded superiority of human milk seems still to be something of a nutritional mystery.

Some nutritional discoveries seem to have no immediate practical application, although one often wishes that they do. One of the recent discoveries raises the question whether nutritional disturbances in infancy and childhood have a delayed effect and show evidence of deleterious effect late in adult life. Best [17] has found that if young

14. Toverud, K. U.; Jeans, P. C., and Stearns, G.: Unpublished data.

15. Mueller, A. J., and Cox, W. M.: Comparative Nutritive Value of Casein and Lactalbumin for Man, J. Nutrition **34**:285 (Sept.) 1947.

16. Gordon, H. H.; Levine, S. Z.; Wheatley, M. A., and Marples, E.: Respiratory Metabolism in Infancy and Childhood: XX. The Nitrogen Metabolism in Premature Infants—Comparative Studies of Human Milk and Cow's Milk, Am. J. Dis. Child. **54**:1030 (Nov.) 1937. Jeans, P. C., and Stearns, G.: Casein and Lactalbumin as the Sole Source of Protein in Infant Feeding, to be published.

17. Best, C. H., and Hartroft, W. S.: Nutrition, Renal Lesions and Hypertension, Federation Proc. **8**:610 (Sept.) 1949.

rats are deprived of choline for a few days and then the deficiency corrected they seem to recover completely from their brief disturbance but at maturity arteriosclerosis and hypertension develop. Possibly some other early cause may be found for the human being. In any case, whatever the cause of hypertension, it seems to be related in some manner to nutrition.

Rheumatic fever, one of the great crippling conditions of childhood, seems to be related to nutrition as well as infection. Children with rheumatic fever are invariably undernourished and have poor appetites. One of the most satisfactory measures for prevention of recurrences of this disease is restoration and subsequent maintenance of good nutrition. Good environmental care must be a part of such a regimen. Although the relation between nutrition and decrease of recurrence is not clear, clinical studies have shown that a relationship exists.[18]

New and relatively new discoveries in nutrition are legion. It is impracticable even to try to list them. All must be considered as having a bearing, even though remote for some, on practical applications of our nutritional knowledge. Furthermore, our nutritional knowledge is broadening so rapidly that we cannot even guess what tomorrow will bring forth.

18. Jackson, R. L.: Treatment of Acute Rheumatic Fever and Prevention of Recurrences, J. A. M. A. **141**:439 (Oct. 15) 1949.

# GROWTH AND DEVELOPMENT OF NEGRO INFANTS

## II. Relation of Birth Weight, Body Length and Epiphysial Maturation to Economic Status

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THE AVERAGE birth weights previously reported for Negro infants are 100 to 500 Gm. less than those reported for white infants. Since these figures have been based on medically indigent patients, the possible effect of socioeconomic conditions must be considered before the lower birth weights of Negroes can be ascribed to inherent racial factors.

Analysis of birth weights at Freedmen's Hospital gave higher averages than did analyses of other series on Negro infants.[1] Knowing no other explanation for this fact, we assumed it to be due to the better economic status of Negroes in the District of Columbia.

In the present study we have attempted to determine the effect of economic status on birth weight, body length and osseous maturation of newborn Negro infants. The epiphysial centers chosen for study were the distal femoral and proximal tibial, since these begin to calcify a few weeks before or after term.

### METHOD OF STUDY

The subjects for study were 300 normal newborn Negroes (164 male and 136 female) born in the maternity service of Freedmen's Hospital between March 1948 and September 1949. All were single born, and all weighed 5 pounds (2,268 Gm.) or more. Infants whose mothers had recognized complications of pregnancy were excluded. All mothers had negative serologic reactions for syphilis at the time of delivery.

For evaluation of economic status patients were grouped according to hospital pay status into the following groups: (1) private patients delivered by members of the obstetric staff, (2) patients in the ward service who were paying for hospitalization and (3) free or indigent patients.

The mothers were questioned regarding diet during pregnancy. Although the protein intake of about 10 per cent of them appeared to be grossly inadequate, we felt that we could make no reliable estimate of the amount of protein ingested.

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From the Department of Pediatrics, Howard University School of Medicine, and the Pediatric Service of Freedmen's Hospital.

1. Scott, R. B.; Jenkins, M. E., and Crawford, R.: Growth and Development of Negro Infants: I. Analysis of Birth Weights of 11,818 Newborn, to be published.

Information concerning vitamins and calcium was also considered inaccurate. The only dietary information utilized was the milk intake. We compared two groups: (1) those whose average milk intake had been 1 quart (1,000 cc.) or more daily throughout pregnancy and (2) those who had had an average of less than 1 pint (473 cc.) daily throughout pregnancy. About half of the latter group had had almost no milk.

A roentgenogram of each infant's right knee was taken in the posteroanterior position on the second or third day of life. The same technic was used for all in order that the measurements might be comparable. The following technical factors were used: peak kilovoltage, 40; milliamperage, 40; distance, 35 inches (89 cm.), and time, 1/20 second. The two diameters of each distal femoral and proximal tibial epiphysis were measured to the nearest 0.5 mm. with a sliding caliper scale. In cases in which the calcified area was under 2 mm. the measurements were less accurate, since beginning calcification was frequently irregular in shape.

## RESULTS

The mean birth weights corresponded rather closely with the upper limits of those previously reported for full term Negro infants[2] but were not strictly comparable, since we included infants weighing between 5 and 5½ pounds (2,268 and 2,500 Gm.), who are usually classified as premature.

In every infant in whom the tibial center was present, the femoral center was present also. In most of the infants the femoral center was the larger of the two, but in a few the tibial center was slightly larger.

The femoral center was present in 96 per cent of the girls and 92 per cent of the boys. The tibial center was present in 74 per cent of the girls and 67 per cent of the boys. Absence of the centers was noted in a few of the larger infants, the heaviest infant without either center being a 9½ pound (4,260 Gm.) boy and the heaviest without the tibial center a 10 pound (4,530 Gm.) girl (charts 1 and 2).

The mean size of both centers increased with increasing birth weight and crown-heel length (charts 1 to 6).

The relation of size of centers to sex is also apparent, the centers being definitely larger in girls than in boys of the same weight or length (charts 5 and 6). This sex difference is less apparent in the larger infants.

When cases were analyzed according to economic status (chart 7) the boys in the indigent group were found to weigh about 200 Gm. less than the boys in the other two groups and to have correspondingly smaller centers. No such difference was noted in the girls.

Since first-born infants constituted a larger percentage of the infants in the private group than in the other two groups, these infants

2. Palmer, C. E., and Ciocco, A.: Somatic Status at Birth, in the Mitchell-Nelson Textbook of Pediatrics, edited by W. E. Nelson, ed. 4, Philadelphia, W. B. Saunders Company, 1946, p. 14. Bakwin, H.: The Negro Infant, Human Biol. 4:1, 1932.

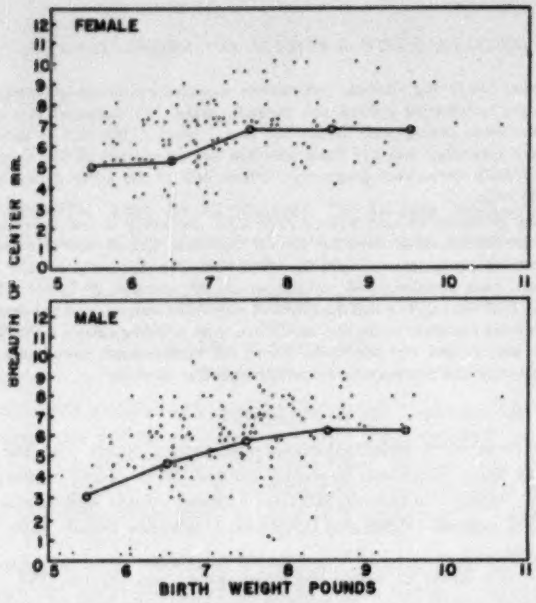


Chart 1.—Relation of birth weight to breadth of distal femoral ossification center. The mean breadth of the center increases with increasing birth weight.

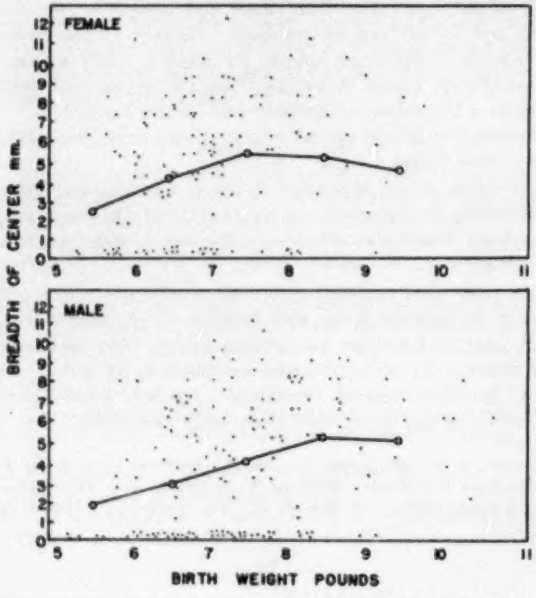


Chart 2.—Relation of birth weight to proximal tibial ossification center. The mean breadth of the center increases with increasing birth weight.

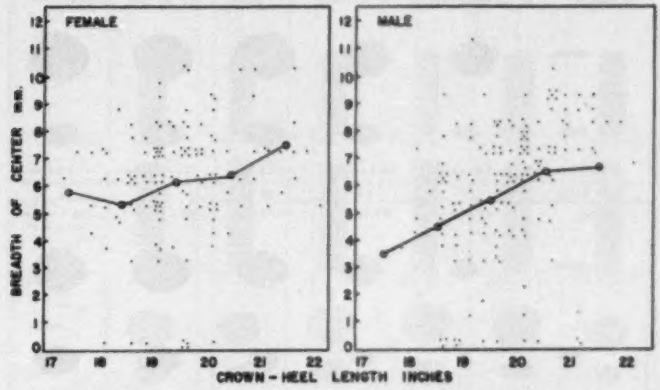


Chart 3.—Relation of body length to breadth of distal femoral ossification center. The mean breadth of the center increases with increasing body length.

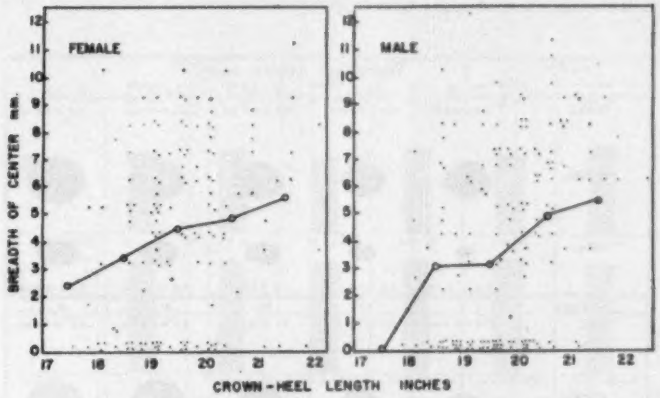


Chart 4.—Relation of body length to breadth of proximal tibial ossification center. The mean breadth of the center increases with increasing body length.

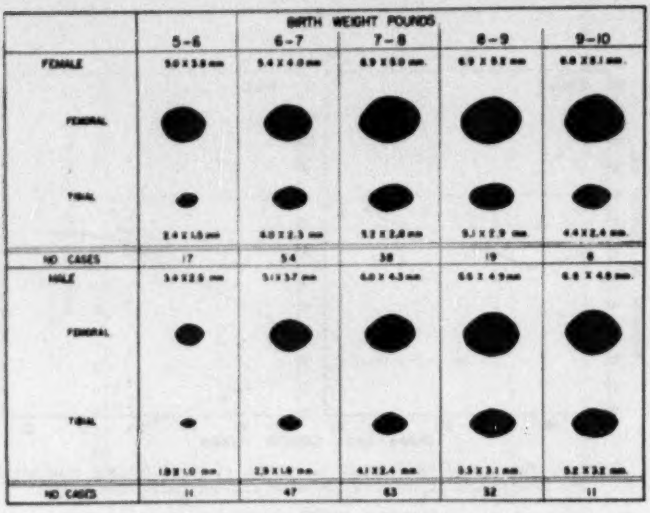


Chart 5.—Relation of birth weight to size of epiphysial ossification centers. The mean size of both centers increases with increasing birth weight and is greater in girls than in boys of the same birth weight.

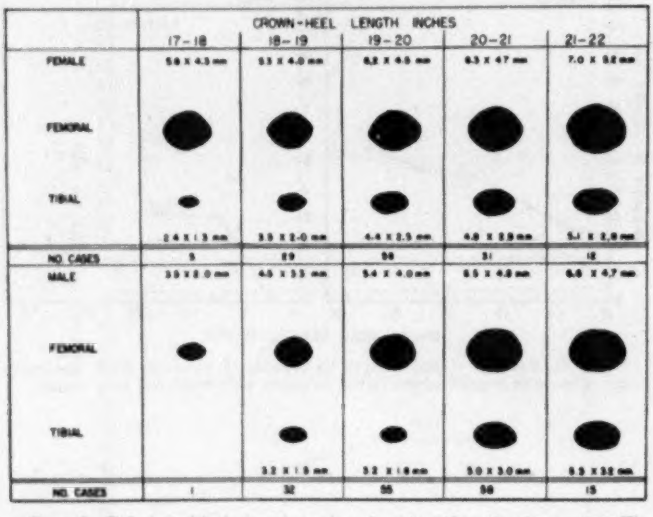


Chart 6.—Relation of body length to size of epiphysial ossification centers. The mean size of both centers increases with increasing body length and is greater for girls than for boys of the same weight.

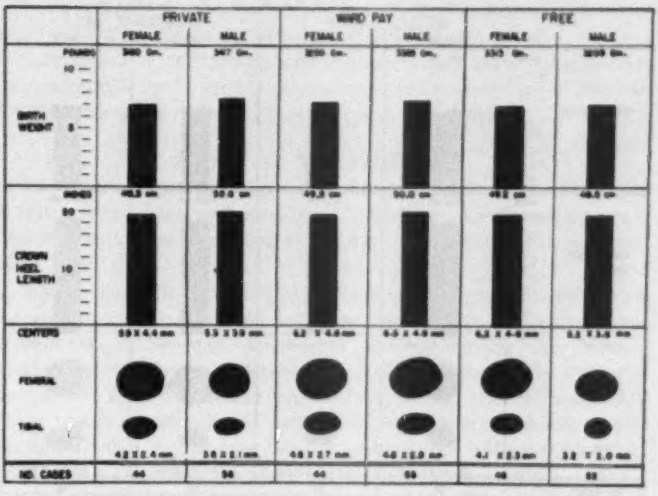


Chart 7.—Relation of body dimensions and size of epiphysial ossification centers to economic status. Birth weight, body length and size of centers of the entire group show no significant variation with economic status.

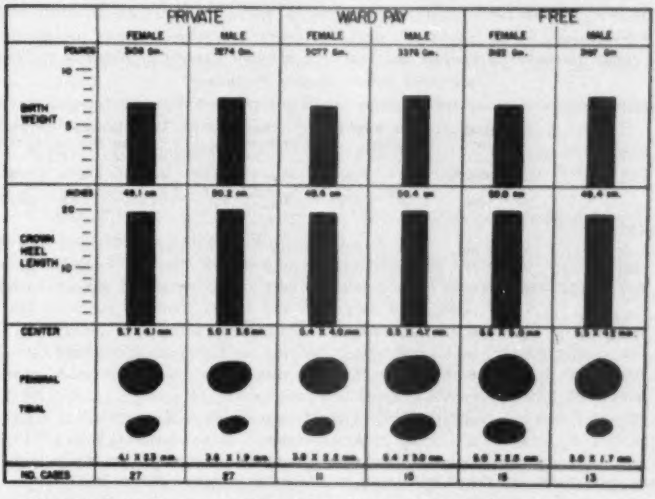


Chart 8.—Relation of body dimensions and size of epiphysial ossification centers of first-born infants to economic status. Birth weight, body length and size of centers of first-born infants show no significant variation with economic status.

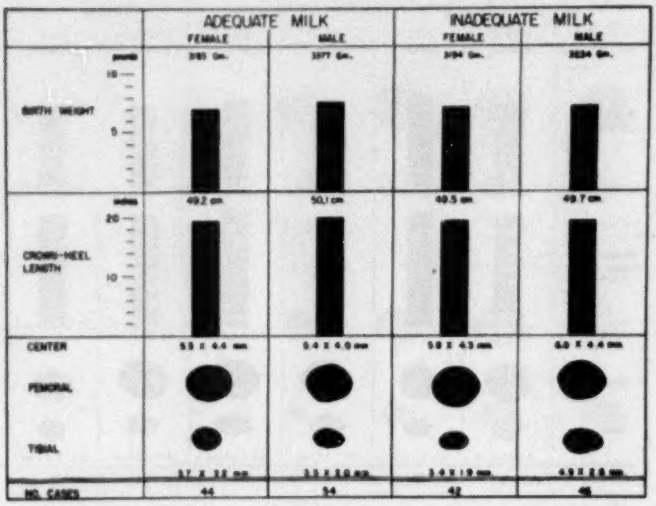


Chart 9.—Relation of body dimensions and size of epiphysial ossification centers to milk intake during pregnancy. Birth weight, body length and size of centers show no relation to milk intake during pregnancy.

*Mean Birth Weights, Crown-Heel Lengths and Size of Epiphysial Centers in Relation to Economic Status and Milk Intake During Pregnancy**

| | Number of Cases | | Birth Weight, Gm. | | Crown-Heel Length, Cm. | | Distal Femoral Center, Mm. | | Proximal Tibial Center, Mm. | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female |
| Entire series | 164 | 136 | 3,240 | 3,196 | 50.1 | 49.4 | 5.7×4.2 | 6.1×4.5 | 3.9×2.3 | 4.1×2.4 |
| Economic status, all cases | | | | | | | | | | |
| Private | 56 | 44 | 3,417 | 3,160 | 50.6 | 49.5 | 5.3×3.9 | 5.9×4.4 | 3.8×2.1 | 4.2×2.4 |
| Ward pay | 56 | 44 | 3,205 | 3,250 | 50.0 | 49.5 | 6.5×4.8 | 6.2×4.8 | 4.8×2.9 | 4.6×2.7 |
| Free | 52 | 48 | 3,089 | 3,133 | 49.5 | 49.2 | 5.2×3.8 | 6.2×4.6 | 3.2×2.0 | 4.1×2.3 |
| Economic status, firstborn | | | | | | | | | | |
| Private | 27 | 27 | 3,374 | 3,198 | 50.2 | 49.1 | 5.0×3.6 | 5.7×4.1 | 3.6×1.9 | 4.1×2.3 |
| Ward pay | 15 | 11 | 3,276 | 3,077 | 50.4 | 49.4 | 6.5×4.7 | 5.4×4.0 | 5.4×3.0 | 3.8×2.2 |
| Free | 13 | 15 | 3,197 | 3,122 | 49.4 | 49.0 | 5.5×4.2 | 6.6×5.0 | 3.0×1.7 | 5.0×2.8 |
| Milk intake | | | | | | | | | | |
| Adequate | 54 | 44 | 3,277 | 3,183 | 50.1 | 49.2 | 5.4×4.0 | 5.5×4.4 | 3.5×1.8 | 3.7×2.2 |
| Inadequate | 40 | 42 | 3,234 | 3,194 | 49.7 | 49.5 | 6.0×4.4 | 5.8×4.3 | 4.9×1.9 | 3.6×1.9 |

* Birth weight, body length and size of center show no relation to economic status or milk intake.

were studied separately (chart 8). No consistent variation of weight, length or size of epiphyses with economic status was found.

Comparison of the groups whose mothers had either adequate or inadequate milk intake during pregnancy shows scarcely any difference in body dimensions or size of centers (chart 9 and table).

## REWIEW OF THE LITERATURE

The effect of economic status and antepartum diet on the incidence of prematurity seems well established. However, conflicting opinions have been expressed concerning their effect on the size of the full term infant.

Bakwin and Bakwin,[3] studying a group of newborn white infants of varying economic status, found that those from poverty-stricken environments were smaller in all dimensions. Burke, Harding and Stuart[4] found a significant relation between the protein content of the mother's diet and the birth weight and length of the infant. Ebbs, Tisdall and Scott,[5] observing antepartum patients of low economic status, found that mothers to whom an adequate diet was supplied had fewer obstetric complications and a significantly lower incidence of prematurity. However, the birth weight of full term infants was not affected. Adair and Scammon[6] noted the relation of body dimensions and sex to the presence or absence of epiphysial ossification centers in the newborn. Ossification was more advanced in infants of greater birth weight and length and more advanced in girls than in boys of the same birth weight. Other observers have confirmed these findings.[7] Hess and Weinstock[8] reported that ossification was more advanced in Negro than in white

3. Bakwin, H., and Bakwin, R.: Body Build in Infant: Anthropometry in Newborn, Human Biol. **6**:612, 1934.

4. Burke, B. S.; Harding, V. V., and Stuart, H. C.: Relation of Protein Content of Mother's Diet During Pregnancy to Birth Length, Birth Weight, and Condition of Infant at Birth, J. Pediat. **23**:506, 1943.

5. Ebbs, J. H.; Tisdall, F. F., and Scott, W. A.: Influence of Prenatal Diet on Mother and Child, J. Nutrition **22**:515, 1941.

6. Adair, F. L., and Scammon, R. E.: Ossification Centers of Wrist, Knee, and Ankle at Birth with Particular Reference to Physical Development and Maturity of the Newborn, Am. J. Obst. & Gynec. **2**:35, 1921.

7. Menees, T. O., and Holly, L. E.: Ossification of Extremities in Newborn, Am. J. Roentgenol. **28**:347, 1932. Müller, J. H., and Balbi, J.: Appearance and Development of Ossification Centers in the Newborn, Schweiz. med. Wchnschr. **72**:1013, 1942. Sieberg, C.: Occurrence and Form of Proximal Tibial Epiphysial Centers in Newborn, Klin. Wchnschr. **21**:1105, 1942. Stampfel, K., and Tscherne, E.: The X-Ray Diagnosis of Postmature Birth, Ztschr. f. Geburtsh. u. Gynäk. **119**:31, 1939.

8. Hess, A. F., and Weinstock, M.: A Comparison of the Evolution of Carpal Centers in White and Negro New-Born Infants, Am. J. Dis. Child. **29**:347 (March) 1925.

newborn children, quite apart from factors of sex and birth weight. Dunham, Jenss and Christie[9] reported similar findings. Christie,[10] studying nine ossification centers, found a similar relation between the presence of each center and the birth weight, sex and race of the infant. In his series the only infants under 2,000 Gm. showing calcification of the proximal tibial center were Negro females.

## SUMMARY AND CONCLUSIONS

Roentgenograms were taken of the knees of 300 newborn Negro infants, and the diameters of the distal femoral and proximal tibial epiphyses were measured.

We have confirmed previous observations of the relation of epiphysial maturation to birth weight, body length and sex.

We have not been able to demonstrate any relation between economic status or milk intake during pregnancy and the size of these centers.

Dr. Ethel C. Dunham gave helpful suggestions and criticisms in the preparation of this study. Dr. W. Montague Cobb, professor of anatomy, assisted in methods of measuring epiphyses, and Dr. Eleanor P. Hunt, of the Children's Bureau, assisted in statistical evaluation of data.

9. Dunham, E. C.; Jenss, R. M., and Christie, A.: A Consideration of Race and Sex in Relation to Growth and Development of Infants, J. Pediat. **14**:156, 1939.

10. Christie, A.: Prevalence of Ossification Centers in the Newborn Infant, Am. J. Dis. Child. **77**:355 (March) 1949.

# VITAMIN D INTOXICATION IN A CHILD WITH RHEUMATOID ARTHRITIS

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AND
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HARMFUL and lethal effects resulting from the prolonged administration of large doses of vitamin D used in the treatment of arthritis in adults are well established.[1] The administration of high potency vitamin D in the treatment of rheumatoid arthritis in a child resulting in soft tissue calcification and renal insufficiency, to our knowledge, has not been previously reported. These findings in a patient under our observation prompted this case report and discussion.

## REPORT OF A CASE

G. G., a 12 year old white girl, was admitted to the Research and Educational Hospitals on May 25, 1949, because of painless abdominal enlargement of one month's duration.

The past history revealed that she had "scarlet fever" at 6 months of age, from which recovery was uneventful. When the child was 17 months of age, the mother noted that she began to limp and was unable to move the right knee through a full range of motion. At 18 months the child had a rash, which again was considered to be "scarlet fever." The right knee continued to be the only joint manifesting symptoms until she reached 4 years of age, when within several weeks pain, swelling and limitation of motion of the joints of the hands and feet developed. Pain and limitation of motion of the spine, particularly in the cervical region, developed. The appetite became poor, and gain in weight was slow. The joint deformities gradually became more pronounced, and weakness and easy fatigability developed. High potency vitamin D capsules [2] were given in doses of 2 to 3 capsules (100,000

From the Department of Pediatrics, University of Illinois College of Medicine.

1. (*a*) Donegan, C. K.; Messer, A. L., and Orgain, E. S.: Vitamin D Intoxication Due to Ertron: Report of 2 Cases, Ann. Int. Med. **30**:429-435, 1949. (*b*) Kaufman, P.; Beck, R. D., and Wiseman, R. D.: Vitamin D ("Ertron") Therapy in Arthritis: Treatment Followed by Massive, Metastatic Calcification, Renal Damage and Death, J. A. M. A. **134**:688-690 (June 21) 1947; correction, ibid. **134**:971 (July 12) 1947.

2. The preparation used was arkalyn,® manufactured by the Paul B. Elder Company, Bryan, Ohio. Active constituent is irradiated ergosterol in oil, biologically standardized according to USP XIII methods.

to 150,000 U. S. P. units) orally each day from the development of multiple joint symptoms at 4 years of age to the time of her first admission to this hospital, on March 10, 1947. This was a total of five and one-half years of therapy.

Within a few days after the start of therapy, the mother noticed that the child had definitely increased thirst. She asked for a large glass of water at bedtime, a request which she had never made before. Soon she began to awaken once or twice during each night to urinate and to drink more water. Since then she has required about eight large glasses of water daily. Three weeks after vitamin D therapy was begun, she was relieved of much of her pain. Whereas previously she

Fig. 1.—The patient at 9½ years of age, weighing 33 pounds (15.0 Kg.), height 45 inches (114.30 cm.). Note the muscular atrophy and multiple joint deformities.

was flat on her back in bed with pain, she was then able to get up and go to the toilet by herself for the first time in months. At this time, anorexia developed, and she vomited several times a week. Appetite for sweet foods was lost. She never liked milk, but she drank about two glasses a day. She failed to gain weight while receiving vitamin D therapy, weighing about 33 pounds (15 Kg.) for five years. Her skin became dry and pruritic. Stupor was not noted except for delirium of two days' duration during an episode of pneumonia in March 1945. Sulfonamides were used sparingly because it was recognized that her kidneys had poor function. Attacks of pain, swelling and stiffness in joints continued to occur after infections of the upper respiratory tract.

The family history revealed that the father died of heart trouble in September 1946. The mother, aged 41, was living and well. There were three brothers, aged 13 years, 7 years and 4 months, all in good health. The patient had been immunized against diphtheria but had not had a vaccination for smallpox.

She was first seen by us when she was admitted to the hospital, March 10, 1947, because of pain, swelling and deformity of numerous joints. Physical examination of the child at that time revealed that she was thin and undersized, with multiple joint deformities (fig. 1). Her weight was 33 pounds, and her height was 45 inches (114.3 cm.); both measurements ranked her below the 3 percentile group for her age (Stuart-Meredith charts). The head tilted to the right but could be moved to the left. The cardiac and pulmonary findings were normal. Blood pressure was 98 diastolic and 70 systolic. The spleen was palpable 5 cm. below the left costal margin and was firm. The liver was not palpable. The extremities were very thin; marked muscular atrophy was observed. There was fusiform swelling of all the

Fig. 2.—Fusiform swelling of the joints of the fingers and swelling of the wrists.

joints of the fingers (fig. 2); moderate swelling about the ankles, knees and wrists, with considerable limitation of motion of these joints, was observed. The patient walked with a shuffling gait consisting of very short steps. All the mandibular movements were possible with only slight restriction of range.

The relevant laboratory data are presented in the table.

The roentgenograms indicated narrowing of the joint spaces of the knees, with marked calcification of the popliteal arteries (fig. 3). The lateral aspects of the femoral and tibial epiphyses were irregular in contour, with some soft tissue calcification about the knee. There was moderate soft tissue swelling about the joints. The cervical portion of the spine demonstrated irregular calcification and contour. Roentgenograms of the hands and wrists revealed distortion of the distal portions of the ulna and radius, moderate destruction and deformity of the carpal bones, thinning and irregularity of the epiphyses of the proximal phalanges and marked loss of calcific density throughout all the bones of the hands and forearms. Laminograms of the temporomandibular joints revealed marked decrease in excur-

sion of the condyles, although the degree of opening appeared adequate.[3] The condylar heads were flattened and irregular, more on the left than on the right. The joint spaces appeared to be narrowed. Plain roentgenograms of the abdomen showed calcification of the aorta and of the iliac and femoral arteries. Intravenous pyelography disclosed marked delay in the appearance of the dye, with a suggestion of early caliectasis on the right. The roentgenograms of the chest showed marked increase in bronchovascular shadow on the right with pleural adhesions medially. The cardiac shadow was normal.

*Laboratory Data*

| | March 1947 | May 1949 | June 1949 |
|---|---|---|---|
| Blood pressure, mm./Hg | 98/70 | 174/124 | 190/130 |
| Erythrocytes | 4,350,000 | 4,000,000 | .... |
| Hemoglobin, Gm./100 cc. | 12.5 | 12.0 | .... |
| Leukocytes | 7,000 | 5,000 | 4,000 |
| Sedimentation rate, mm./hr. (Wintrobe) | 20 | 14 | .... |
| Congo red, per cent disappeared from blood | .. | 26 | .... |
| Urine | | | |
| Albumin | 1+ | 1+ | 3+ |
| Microscopic appearance | Normal | Normal | Normal |
| Sulkowitch reaction | 2+ | Negative | Negative |
| Maximum specific gravity | 1.015 | .. | 1.015 |
| Phenolsulfonphthalein, per cent excreted in two hours | 15 | .. | 35 |
| Urea clearance,* per cent of normal | 74 | .. | 56 |
| Inulin clearance,* per cent of normal | .. | 40 | 46 |
| Paraaminohippurate clearance,* per cent of normal | .. | 31 | 27 |
| Blood | | | |
| Nonprotein nitrogen, mg./100 cc. | 41 | 36 | 37 |
| Urea nitrogen, mg./100 cc. | 14.5 | 19 | 30 |
| Uric acid, mg./100 cc. | .. | .. | 3.8 |
| Creatinine, mg./100 cc. | .. | .. | 1.8 |
| Carbon dioxide content, mM./liter | .. | .. | 23.7 |
| Serum | | | |
| Calcium, mg./100 cc. | 13.1 | 8.7 | .. |
| Phosphorus, m./100 cc. | 4.0 | 4.2 | .. |
| Alkaline phosphatase, Bodansky units | 4.3 | 3.5 | .. |
| Sodium, mEq./liter | .. | .. | 136 |
| Potassium, mEq./liter | .. | .. | 4.73 |
| Chloride, mEq./liter | .. | .. | 106 |
| Proteins, Gm./100 cc. | 8.0 | 6.9 | .. |
| Albumin, Gm./100 cc. | 4.9 | 4.2 | .. |
| Globulin, Gm./100 cc. | 3.1 | 2.7 | .. |
| Cephalin flocculation, 48 hours | 1+ | .. | Negative |
| Thymol turbidity, units | .. | .. | 9.5 |
| Response to epinephrine | | | |
| Increase in uric acid-creatinine ratio, per cent | .. | .. | 26.5 |
| Reduction in eosinophils, per cent | .. | .. | 86.0 |
| Wassermann reaction | Negative | .. | .. |
| Mantoux reaction | Negative (1:10,000) | .. | Negative (1:1,000) |

* Corrected for a surface area of 1.73 meters.

Her progress in the hospital was marked by a recurrent low grade febrile course. The use of vitamin D was discontinued on admission. Physical therapy was given to increase motion of the joints. Transient swelling of the right temporomandibular joint occurred, and she complained of occasional pains in the heels. Excessive thirst and nocturia were noted. She weighed 35½ pounds (16.1 Kg.) on discharge, July 22, 1947.

3. More detailed description of the involvement of the temporomandibular joint of this patient has been presented elsewhere (Engel, M. B.; Richmond, J. B., and Brodie, A. G.: Mandibular Growth Disturbances in Rheumatoid Arthritis of Childhood, Am. J. Dis. Child. **78**:728 [Nov.] 1949, case 5).

After the patient's discharge, there was no recurrence of arthralgia. Stiffness of joints and irritability were present in the early morning. As the day progressed, the "joints would loosen up and she became her normal cheery self." She was unable to extend the arms completely or to stoop over. She continued to walk with a shuffling gait.

Fig. 3.—Roentgenograms demonstrating the narrowing of the joint spaces of the knees (*A*, right, and *B*, left) with marked vascular calcifications of the popliteal arteries. The lateral aspects of the epiphyses are irregular in contour. Soft tissue calcification is present about the knee.

During November 1947, she had pneumonia, which responded satisfactorily after eight days of penicillin therapy. She was seen at infrequent intervals by the family physician. In April 1949, a check-up examination revealed a 4+ reaction for albumin in the urine. Two weeks later, she complained of a sore throat and had a temperature of 102 F. for four days. During this time the abdomen began to

enlarge. The child's slacks were "let out" to adjust to her increasing abdominal circumference. She gained 3 pounds (1.3 Kg.) in two weeks. She had no edema of the extremities or eyelids.

Her appetite was fair. She did not have vitamin supplements after her return home. Excessive thirst and polyuria continued, and nocturia persisted despite the discontinuance of vitamin D therapy.

Physical examination on May 25, 1949 showed the continued presence of emaciation and multiple skeletal deformities in this 12 year old girl. She was cooperative and cheerful. Her temperature was 99.4 F., weight 46 pounds (20.9 Kg.) and height 52½ inches (133 cm.). Her blood pressure was 168 systolic and 114 diastolic. The skin was dry. There was mild generalized lymphadenopathy. Several carious teeth were noted. The heart and lungs were normal. Slight shifting dulness and a minimal fluid wave were noted in the moderately protuberant abdomen. The liver was palpable 2 cm. below the right costal margin. The spleen was felt 4 cm. below the left costal margin. The genitalia were those of an immature female, with scanty pubic hair.

There was full flexion at the elbows, but extension was limited to 160 degrees bilaterally. Flexion of the fingers was moderately restricted. The phalangeal, metacarpophalangeal and wrist joints presented knobby enlargement bilaterally. The knee joints had complete range of motion. There was bilateral hallux valgus with marked adduction of the great toes. No edema was detected. Reflexes were equal and hyperactive.

Ophthalmologic examination with the slit lamp revealed a whitish ring of opacification along the limbus of the cornea bilaterally. It appeared to lie superficially, mostly in Bowman's zone, and was limited to the interpalpebral area both temporally and nasally. There were numerous small calcareous deposits in the bulbar conjunctivas and also in the interpalpebral zones. Funduscopic study showed the margins of the disks to be mildly blurred and the vessels slightly arched over the margins. The vessels presented variation in the caliber of the arterioles with tortuosity and dipping, arteriovenous compression and disproportion (1:3). Vision was 20/17, bilateral and uncorrected. These findings were interpreted to be grade II hypertensive retinopathy and calcareous deposition in the corneas and conjunctivas, probably representing further evidence of hypervitaminosis D.

Roentgenograms of the cervical portion of the spine showed the vertebral bodies to be abnormally straightened; a roentgenogram of the chest revealed a moderate obstructive emphysema of the left lung for which bronchoscopy could demonstrate no definite cause, and arthritic changes of the shoulder joints were observed. A roentgenogram of the abdomen demonstrated enlargement of the spleen, calcification of the abdominal aorta, renal, iliac and femoral arteries and sclerosis of the acetabular margins with loss of joint space in both hips. Lateral views of the knees in flexion revealed calcified vascular shadows in the popliteal fossae. The bones were demineralized, the joint spaces decreased and the joint surfaces were irregular; views of the hands showed spotty demineralization throughout with loss of joint space and destruction of joint surfaces and bony substances in the region of the joints. A barium swallow revealed no esophageal varices.

The pertinent laboratory data at this time are recorded in the table.

*Hospital Course.*—The patient continued to be free of pain. Nocturia was especially notable. The abdominal enlargement remained unchanged, but peripheral edema was not observed. On repeated examinations her blood pressure was shown to range between 176 systolic and 114 diastolic and 190 systolic and 130 diastolic.

The venous pressure was 110 mm. of water in the antecubital vein. The child remained afebrile; she was permitted unlimited activity and was discharged June 11, 1949.

*Résumé.*—This is a report on a 12 year old white girl who has had rheumatoid arthritis since infancy. She received an irradiated ergosterol preparation in large doses for five and one-half years, with the subsequent development of anorexia, vomiting, polydipsia, polyuria, nocturia, calcification of blood vessels, periarticular soft tissue, conjunctivas and corneas, hypertension, hypertensive retinopathy and renal insufficiency. After the discontinuance of vitamin D therapy, some amelioration of her symptoms was noted, but there was no significant improvement in renal function after two years of observation, indicating irreversible kidney damage.

## COMMENT

*Physiologic Action of Vitamin D.*—A survey of the literature [4] reveals that no completely satisfactory explanation of the physiologic action of vitamin D in antirachitic or massive dosages has been formullated. The disorder resulting from the prolonged administration of huge doses of the vitamin has been considered by Tumulty and Howard [5] to be a hypervitaminosis. Some consider it to be poisoning, assuming that vitamin D in massive doses has toxic properties which cause necrosis and subsequent calcification of tissues. Albright and Reifenstein [6] ascribed the manifestations of hypervitaminosis D to an exaggeration of one or both of the known actions of vitamin D: (1) to increase absorption of calcium from the gastrointestinal tract and (2) to increase excretion of phosphorus in the urine. The first of the two properties probably plays the chief role when vitamin D is used in excess. Tissue necrosis according to these authors is not due to a toxic property of vitamin D but is secondary to the precipitation of calcium phosphate in the tissues. Reed [4b] expressed the opinion that tissue injury must occur first, however. The probable sequence of events is increased calcium absorption, increased serum calcium level, decreased parathyroid activity, decreased urinary phosphorus excretion, increased serum phosphorus level, supersaturation of the blood with respect to calcium phosphate and precipitation of the calcium at abnormal sites.

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4. (*a*) Reed, C. I.; Struck, H. C., and Steck, I. E.: Vitamin D: Chemistry, Physiology, Pharmacology, Pathology, Experimental and Clinical Investigations, Chicago, University of Chicago Press, 1939. (*b*) Reed, C. I.: Vitamin D and Tissue Calcification, Am. Pract. & Digest Treat. **1**:164, 1950.

5. Tumulty, P. A., and Howard, J. E.: Irradiated Ergosterol Poisoning: Report of 2 Cases, J. A. M. A. **119**:233-236 (May 16) 1942.

6. Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease: Selected Studies, Baltimore, Williams & Wilkins Company, 1948, p. 95.

Freeman, Rhoads and Yeager [7] studied the effect of 100,000 U. S. P. units of vitamin D (ertron®) daily on the calcium balance of a 9 year old boy with rheumatoid arthritis. There was an increased urinary excretion of calcium and decreased calcium retention on both high and low calcium diets. On the high calcium diet, albuminuria developed; this had never been present before, and it cleared up one week after administration of vitamin D was discontinued. The serum calcium was not elevated at the end of the metabolic study. These findings demonstrate that increased urinary calcium excretion and conditions favorable to the deposition of calcium in the kidney may precede, and need not be accompanied with, hypercalcemia. The toxicity of vitamin D can be explained by its effect on calcium and phosphorus metabolism and on renal function.

*Clinical and Laboratory Findings.*—Debré [8] reported the toxic effects of overdoses of vitamin D in 21 children, some of which were serious, causing death of 2 patients. Some of the children had received large amounts of vitamin D prescribed to accelerate the healing of tuberculosis. Typical symptoms observed were anorexia, nausea and vomiting, excessive thirst associated with polyuria and constipation alternating with diarrhea. Other features noted were headache and pain in the abdomen, back and extremities, associated with stiffness and muscular cramps. If use of the drug was not discontinued, the child soon became pale out of proportion to the anemia. There was loss of weight, the skin and mucous membranes became dry and weakness and irritability developed. At times the temperature was elevated. Finally, stupor and deep breathing occurred and death followed.

The most important group of symptoms is related to disturbances of renal function, notably the appearance of calcium in abnormal amounts and of calcium-containing casts in the urine, albuminuria and finally fixation of the specific gravity at low levels, together with signs of renal insufficiency. An early sign of danger is a persistently positive result of the Sulkowitch test.[9] The unfavorable prognosis of high blood pressure and of a high blood urea nitrogen level has been emphasized by Debré.

There is frequently a low erythrocyte count. The serum calcium is usually high, ranging between 12 and 21 mg. per hundred cubic centimeters. With uremia, the blood urea, sulfate, creatinine and phosphorus levels are elevated and the calcium levels decreased.

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7. Freeman, S.; Rhoads, P. S., and Yeager, L. B.: Toxic Manifestations Associated with Prolonged Ertron Ingestion, J. A. M. A. **130**:197-202 (Jan. 26) 1946.

8. Debré, R.: Toxic Effects of Overdosage of Vitamin $D_2$ in Children, Am. J. Dis. Child. **75**:787-791 (June) 1948.

9. Barney, J. D., and Sulkowitch, H. W.: Progress in the Management of Urinary Calculi, J. Urol. **37**:746-762, 1937.

Roentgenograms may show bony atrophy and destruction from hypervitaminosis D. Calcium deposits may be seen in the kidneys, bronchi and alveoli, gastric mucous membranes, blood vessels and periarticular tissues.

Walsh and Howard [10] and Fleischner and Shalek [11] have described calcium deposits in the superficial layers of the periphery of the cornea, most marked at the palpebral fissures (band keratitis). These may be seen under direct vision without magnification in patients with prolonged hypercalcemia. Biomicroscopy also may reveal crystalline calcium deposits in the deep conjunctivas of the palpebral fissure in patients with chronic hypercalcemia.

*Factors Contributing to Toxicity.*—The dose of irradiated ergosterol in this case for a 5½ year old child was between 6,000 and 10,000 U. S. P. units per kilogram of body weight per day. Gordon and Sevringhaus [12] have pointed out that toxicity does not depend entirely on the size of the dose. There is a wide range of threshold of toxicity in human beings. The result depends on multiple factors. According to these authors, the factors are (1) the dose per unit of body weight; (2) the duration of administration; (3) the composition of the diet in both mineral and organic matter; (4) the state of the alimentary tract; (5) individual susceptibility; (6) age; (7) preexisting pathologic conditions; (8) the vehicle in which the vitamin is administered; (9) the route of administration; (10) the functional state of the endocrine system; (11) the purity of the vitamin preparation, and (12) the source of the vitamin. Additional factors, yet unknown, are also suggested.

*Differential Diagnosis.*—Early hypervitaminosis D usually raises the serum calcium level. Donegan, Messer and Orgain [10] pointed out that in hyperparathyroidism with definite changes in the bone the serum alkaline phosphatase is elevated. The absence of this finding in hypervitaminosis D may be a helpful diagnostic point. These authors also indicated that intoxication from the administration of massive doses of vitamin D is more widespread than the reports in the literature would appear to indicate, for it may masquerade as renal disease. They presented 2 cases to demonstrate disturbances in calcium-phosphorus metabolism with serious renal damage. The history of massive ingestion of vitamin D is most important in the differential diagnosis.

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10. Walsh, F. B., and Howard, J. E.: Conjunctival and Corneal Lesions in Hypercalcemia, J. Clin. Endocrinol. **7**:644-652, 1947.

11. Fleischner, F. G., and Shalek, S. R.: Conjunctival and Corneal Calcification in Hypercalcemia: Roentgenologic Findings, New England J. Med. **241**:863-865, 1949.

12. Gordon, E. S., and Sevringhaus, E. L.: Vitamin Therapy in General Practice, Chicago, The Year Book Publishers, Inc., 1940, p. 128.

*Pathology of Vitamin D Intoxication.*—Metastatic calcification has been defined [13] as a condition in which calcium salts are deposited in tissues previously normal but with a tendency toward an alkaline reaction. This term implies a transference of calcium from the skeleton to the soft tissues.

The net result of excessive doses of vitamin D is retention of calcium and phosphorus, so that the solubility constant of both ions is relatively easily exceeded and precipitation of both occurs in those soft tissues susceptible to metastatic calcification. Susceptible tissue exists where there is a reduction of tissue concentration of hydrogen ions, phosphatase activity and tissue injury due to the initial calcific changes, such as may be produced by the toxic action of irradiated ergosterol. Ham and Portuondo [14] suggested that, although the calcifications of hypervitaminosis D may be explained by the shift in the calcium from the blood to the tissues, it is possible that other features of the lesion, such as necrosis and infiltration by inflammatory cells, may be caused primarily by a disturbance in the calcium balance between the cells and tissue fluids; this balance conceivably is disturbed on the upswing of the serum calcium curve because of the withdrawal of calcium from the tissues. The cause of the calcification may not be identical with the cause of the necrosis and infiltration by inflammatory cells.

The calcium deposition may be found in any of the soft tissues; the blood vessels, kidneys and lungs are especially susceptible to calcification. Bauer and Freyberg [15] observed that the renal calcification seemed to be primarily in arterioles, the tubular and glomerular involvement being secondary. Microscopic study often reveals that the basement membrane of the cells of the distal tubules is necrotic and calcified. Desquamation occurs, giving rise to obstruction of the tubules, which contributes to the picture of uremia.

Abnormal matrix formation accompanying degenerative or inflammatory changes in tissues establishes sites of affinity for calcium in the presence of normal calcium levels in body fluids. This is observed commonly in hematoma and bursitis and may be a contributing factor when metastatic calcification is observed in rheumatoid arthritis.

Toxic effects may result from vitamin D or related sterols. The purest crystalline preparations of vitamin D may give rise to disturbances of calcium metabolism.[8]

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13. Mulligan, R. M.: Metastatic Calcification, Arch. Path. **43**:177-230 (Feb.) 1947.

14. Ham, A., and Portuondo, B. C.: Relation of Serum Calcium to Pathologic Calcifications of Hypervitaminosis D, Arch. Path. **16**:1-14 (July) 1933.

15. Bauer, J. M., and Freyberg, R. H.: Vitamin D Intoxication with Metastatic Calcification, J. A. M. A. **130**:1208-1215 (April 27) 1946.

Rosenberg, Baggenstoss and Hench [16] were unable to demonstrate lesions specifically diagnostic of rheumatoid arthritis in the kidneys. In a high percentage of their 30 cases, evidence of glomerular endothelial proliferation was present. Thus we may postulate that unrecognized subclinical glomerulitis may have enhanced the toxic effects of the drug in the patient under consideration. When vitamin D is used in large doses, the study of renal function before and after treatment should be carried out. With early detection of excess vitamin D the toxic effects are reversible if use of the drug is discontinued.[16]

The symptomatic improvement which is related to the sedative effect of hypercalcemia probably warranted experimentation with massive dosage of vitamin D for rheumatoid arthritis in the past. The present knowledge of the toxic effects produced in this manner and the recent information concerning endocrine factors in rheumatoid arthritis should invalidate massive vitamin D therapy.

SUMMARY

The effect of large doses of vitamin D has been observed in a 12 year old girl with rheumatoid arthritis. Daily doses of 100,000 to 150,000 U. S. P. units of a proprietary irradiated ergosterol product were given for five and one-half years.

Toxic manifestations of renal insufficiency and metastatic calcification of the soft tissues were observed. The salient features of intoxication resulting from the prolonged use of large doses of vitamin D are discussed.

16. Rosenberg, E. F.; Baggenstoss, A. H., and Hench, P. S.: Causes of Death in 30 Cases of Rheumatoid Arthritis, Ann. Int. Med. **20**:903-919, 1944.

# TOXIC LESIONS OF THE PANCREAS

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IT IS COMMON knowledge that the pancreas may be involved in a number of infectious diseases, among which epidemic parotitis and scarlet fever are the best known. In addition to these, different conditions affecting the digestive tract, such as dysentery, typhoid, spirochetal jaundice, atrophy and infantile diarrhea, and recently uremia, have been reported to cause pancreatic lesions and dysfunction. However, the true nature of the lesions and the underlying morphologic changes still constitute a problem. According to some authors,[1] these changes consist of hemorrhages and necrosis of the parenchyma. Degeneration of the parenchyma with ensuing fibrosis [2] has also been described, as well as atrophy and disorganization of acini [3] and acinar dilatation, leading to a picture similar to cystic fibrosis.[4]

When one considers the number of observations on surgical and autopsy material and the apparent contradictions in the findings, it is astonishing that data relating functional disturbances with morphologic changes and the experimental elucidation of the problem are still lacking. An attempt was therefore made to study the question both in children and experimentally.

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1. Eichhorst, H., in Eulenburg, A.: Real-Encyclopädie der gesammten Heilkunde, Leipzig, Urban & Schwarzenberg, 1880-1881, vol. 2, p. 435. Dieckhoff, C.: Inaug. Dissert., Rostock, 1894. Schlesinger, E.: Inaug. Dissert., Berlin, 1913. Gruber, G. B.: Die Bauchspeicheldrüse, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 5, p. 631.

2. Gross, F.: Pankreasatrophien im Säuglings- und Kindesalter, Jahrb. f. Kinderh. **112**:251, 1926.

3. Gambill, E. E.; Comfort, M. W., and Baggenstoss, A. H.: Chronic Relapsing Pancreatitis, Gastroenterology **11**:1, 1948.

4. Baggenstoss, A. H.: The Pancreas in Uremia: A Histopathologic Study, Am. J. Path. **24**:1003, 1948. Mallory, T. B., in discussion on Baggenstoss, A. H.: The Pancreas in Uremia, ibid. **23**:908, 1947.

## CLINICAL OBSERVATIONS

The results of our functional observations have already been reported in other papers.[5] Investigations made on 280 patients revealed that decrease or abolition of the output of enzymes was commonly observed in scarlet fever, gastritis, nonamebic enteritis, infantile diarrhea and other diseases, whereas a number of other conditions, such as measles, diphtheria, whooping cough, pneumonia and simple undernutrition, did not seem to affect pancreatic secretion. The inhibition of output of enzymes was not coincident with fever and seemed to be easily reversible, because pancreatic function was soon restored to normal after grave symptoms of disease had subsided.

As to the morphologic changes in the pancreas, only little information could be gained from this case material. In the few fatal cases, the pancreas of several patients had to be discarded either because post-mortem changes had occurred or because the lesions could not be evaluated owing to the deficient diets that had been fed to the patients. However, of the 6 patients on whom reliable examinations were performed—3 infants with dysentery and 3 with infantile diarrhea—the pancreas of 3 showed necrotic foci with signs of both regeneration and beginning fibrosis in addition to dissociation of the glandular tissue (fig. 1 *A*). In 1 instance a patch consisting of dilated acini (fig. 1 *B*) was found, together with some interstitial fibrosis. The islets remained of normal appearance in all instances.

## EXPERIMENTAL OBSERVATIONS

In order to gather more information about the pancreatic response to toxic agents, experiments were performed on animals.

Male albino rats of the same strain, ranging in weight from 140 to 190 Gm., were used. They were fed a well balanced diet with a supplement of cod liver oil with added vitamin A and a generous dose of all water-soluble vitamins. Neither the daily amount of food nor the water was restricted.

An attempt was first made to induce pancreatic lesions with paradysentery toxin.[6] The toxin was prepared from twenty-four hour cultures of a standard mixture of different strains of Shigella paradysenteriae (Flexner). The culture was diluted with distilled water until no viable organisms remained and then filtered through a Seitz filter. One milliliter of the filtrate corresponded to 10,000,000,000 organisms.

The toxicity of the filtrate was established in preliminary experiments. The temperature of the animals was taken and white blood cell counts made twice

5. (*a*) Véghelyi, P. V.: Pancreatic Function in Different Clinical Conditions, in the Transactions of the Fifth International Congress of Pediatrics, New York, 1947, Acta pædiat. **36**:483, 1948; (*b*) Pancreatic Function in Toxicosis, Pædiat. danub. **5**:239, 1949.

6. Dr. B. Serény, of the Hungarian State Hygienic Institute, prepared the toxin.

before and at half-hour intervals after the toxin had been administered peritoneally. It was planned to take as the lowest toxic dose that quantity which was followed by a decrease of more than 0.5 degree (C.) in the temperature and a fall of more than 20 per cent in the white blood cell count for at least an hour. However, the

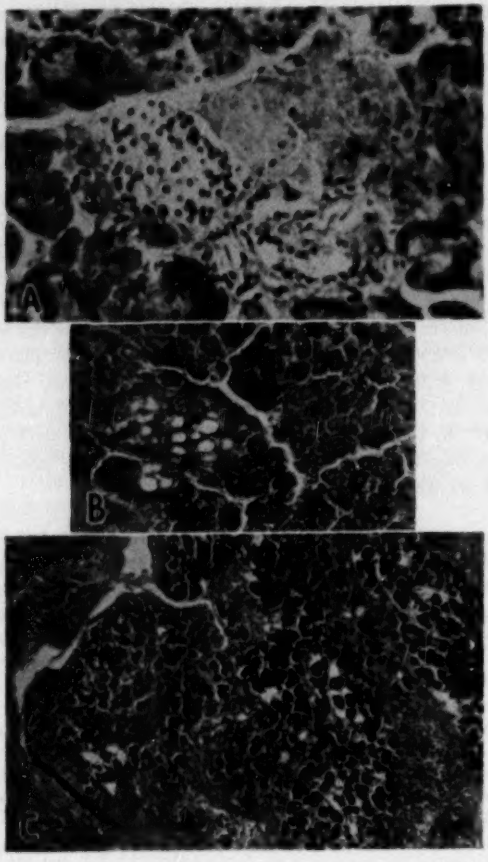


Fig. 1.—*A*, pancreas from infant aged 9 months who died of acute dysentery. Necrotic area with occasional signs of regeneration and normal islet of Langerhans is shown. Hematoxylin and eosin stain; Zeiss apochromatic lens, 8 mm. *B*, pancreas from infant aged 6 months who died of dysentery. Dilatation of acini is shown. Hematoxylin and eosin stain; Zeiss apochromatic lens, 16 mm. *C*, pancreas from rat killed forty-eight hours after injection of dysentery toxin. Necroses and dissociation of parenchyma are shown. Hematoxylin and eosin stain; Zeiss apochromatic lens, 16 mm.

individual rats varied greatly in resistance, and the effective dose could not be determined with more precision than between 0.3 and 0.9 ml. Therefore it was decided to consider 0.7 ml. the lowest toxic dose. (There were extreme variations in the toxicity of different bacterial filtrates and even greater ones in the susceptibility of different strains of rats.)

Twenty-six rats of the same strain as those used in the previous experiment were divided into six groups, and a certain dose of the toxin was administered once intraperitoneally to three groups and once daily to the other three groups. The rats were killed by stunning six, twenty-four, forty-eight and ninety-six hours and ten and fifteen days following the last injection. The results are summarized in table 1.

There could be no doubt that necroses of more or less extent were produced by the toxin, and the results seemed to indicate that the lesions had an unusual tendency to heal. There was, however, little connection between the dose of the toxin administered and the extent and gravity of the lesions. For example, the necrosis observed two days after a

TABLE 1.—*Pancreatic Lesions Induced by Paradysentery Toxin*

| Toxin, Ml. | Days | Hours After Last Injection * | | | | | |
|---|---|---|---|---|---|---|---|
| | | 6 | 24 | 48 | 90 | 240 | 360 |
| 0.7 | 1 | 0 | 0 | D? | .. | .. | .. |
| 2.1 | 1 | N | 0 | DN† | 0 | .. | .. |
| 4.2 | 1 | 0 | DN | N | N | 0 | .. |
| 0.7 | 2 | 0 | D | 0 | DN | .. | .. |
| 2.1 | 2 | N | N | DN | 0 | .. | .. |
| 4.2 | 3 | NH | 0 | DN | N | DF | 0 |

* Explanation of symbols: 0, indicates normal conditions; D, dissociation; N, necrosis; H, hemorrhage; F, fibrosis.
† Figure 1 C.

single dose of 2.1 ml. (fig.1 *C*) was far severer than that observed after twice that amount had been given. Further, no changes whatever were found in the twenty-four hours following administration of the largest dose for three consecutive days, whereas the mildest lesion of the whole series was produced by 2.1 ml. of toxin administered three times. Hemorrhage was found in 1 instance only, and its cause remained unknown. Since only 3 rats were left alive more than four days, it was impossible to ascertain why in 1 animal recovery was accompanied with fibrosis and in the other 2 there were no traces of fibrosis.

Changes in the liver—cloudy swelling and necrosis of the center of the lobule—also did not occur with regularity. Apparently both more toxin and more time were required to induce them than to induce lesions in the pancreas, for in several animals with pancreatic lesions hepatic damage was not detectable. On the other hand, recovery from the hepatic injury seemed to take less time than was necessary for the disappearance of the pancreatic lesion.

Because of the unstable results and the somewhat contradictory findings, an attempt was made to induce pancreatic lesions by means of chlorinated hydrocarbons instead of bacterial toxin.

Tetrachloroethylene was first used, but it soon became evident that it is not suitable for our purpose because doses less than the lethel dose seldom produced pancreatic lesions. Carbon tetrachloride, on the other hand, proved to be an ideal agent for the induction of pancreatic changes. The minimal toxic dose was established in preliminary experiments; according to the results of these, in the rats that we used a

TABLE 2.—*Pancreatic Lesions Induced with Daily Injections of Carbon Tetrachloride* *

| Daily Dose, Gm./ 100 Gm. Body Weight | Survival, Days | Animal Number | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| 0.02 | 7-14 | 0 | 0 | 0 | .. | .. | .. | .. | .. |
| 0.04 | 7-14 | 0 | 0 | V | .. | .. | .. | .. | .. |
| 0.04 | 15-30 | 0 | 0 | V† | V | .. | .. | .. | .. |
| 0.07 | 5-10 | 0 | 0 | 0 | D | V‡ | V | V | .. |
| 0.07 | 11-20 | 0 | 0 | 0 | V | V | V | C | C |
| 0.07 | 21-40 | +DC¶ | +DC | C‖ | C | C | C | CN | +CF |
| 0.07 | 41-60 | DV | +DC | V | C | +C | +CF | +N | .. |
| 0.07 | 61-80 | +DV | V | C | +C | CF | +CF¶ | +CF | +DCF# |
| 0.07 | 81-100 | D | V | C | +CF** | +CF | +DCF | .. | .. |
| 0.07 | 101-150 | DVF | +DVF | +DCF | +DVCN | .. | .. | .. | .. |
| 0.1 | 7 | 0 | D | V | DV | N | .. | .. | .. |
| 0.2 | 3 | 0 | D | DV | .. | .. | .. | .. | .. |
| 0.2 | 7 | DV | DV | VN | N | .. | .. | .. | .. |
| 0.2 | 21-30 | DV | DN | +DN | .. | .. | .. | .. | .. |
| 0.4 | 19 | +D | +DVC | +VC | .. | .. | .. | .. | .. |
| 0.6 | 12 | +D | +D | +DVCN | +DVN | .. | .. | .. | .. |
| 1.0 | 10-14 | +D | +DVCN | +DVCN | +DVN | +DN†† | +DNF‡‡ | +DF§§ | .. |
| 1.5 | 9-11 | +D | +DVN | +DVN | +DVN | +CN | .. | .. | .. |
| 3.0 | 9 | +DVN | +DVN | +N | +NF | .. | .. | .. | .. |

* Explanation of symbols: 0 indicates normal conditions; D, dissociation; V, vacuolation; C, cystic change (dilated acini); N, necrosis; F, fibrosis; +, died.

† Figure 2 A. ‡ Figure 2 B. ‖ Figure 2 C and 3. ¶ Figure 5 A. # Figure 5 B. ** Figure 5 C. †† Figure 6 A. ‡‡ Figure 6 B. §§ Figure 6 C.

single subcutaneous injection of 0.1 Gm. per hundred grams of body weight sufficed to produce regularly minimal but well marked lesions, namely dissociation or necrosis of at least a small part of the parenchyma. (Experiments performed on different breeds have shown that there are significant differences in the susceptibility of various strains to the poison. A gray rat tolerated 0.30 Gm. per hundred grams of body weight without hepatic or pancreatic lesions, whereas only one-tenth that dose was tolerated by an albino rat of a strain different from that used for the present experiments.) Single doses below 0.04 Gm. per hundred grams of body weight were found not to induce changes and

single doses of 0.09 Gm. per hundred grams of body weight to induce changes only occasionally.

Ninety-six rats of the strain previously used were divided into groups, and carbon tetrachloride in various doses was administered subcutaneously each day until the animals died or were killed by stunning. The results are summarized in table 2.

It is apparent from table 2 that it is possible to produce pancreatic changes at will with carbon tetrachloride. The various lesions observed did not differ in any way from those found at autopsy in patients who had died of certain diseases discussed early in this paper or from lesions produced experimentally with bacterial toxin. The nature of the lesions seemed to depend both on the daily amount of carbon tetrachloride given and on the length of the period of administration.

Doses smaller than 0.07 Gm. per hundred grams of body weight, even if administered every day for a full month, did not regularly produce lesions. The lesion induced was vacuolation of the acinar cells preceded by disappearance of normal zymogen granules from the supranuclear zone and marked eosinophilia of the cells (fig. 2*A*). Only small parts of the parenchyma, mostly patches occupying part of a lobule, were involved in the process.

Carbon tetrachloride in doses of 0.07 Gm. per hundred grams of body weight a day led to similar changes within seven to ten days (fig. 2*B*). After three weeks the lesion regularly observable was a cystic change appearing in the vacuolated areas (fig. 2*C*). As the degeneration proceeded, the acini became widely dilated, their lining flat and almost epithelium-like (fig. 4). At the same time hitherto normal parts of the parenchyma also became eosinophilic and then underwent vacuolation. Thus the affected areas seemed to increase in number and, according to the appearance of the surrounding parenchyma, also in size. In this manner several lobules might become involved in the process within about eight to nine weeks. In the meantime fibroblasts were seen to invade the degenerated patches, now measuring 500 to 3,000 microns. Early stages of fibrosis were occasionally observed to appear before the end of the fourth week, but, as a rule, not before the tenth week, when and after which time fibrosis was the type of lesion dominating the picture. From this time on, only ringlike structures interwoven with some blood vessels and fibrous tissue, together with islets of Langerhans, remained in the shrunken lobules (figs. 5 and 6*A*). The islets were always found to have remained normal throughout the entire process, and their cells still kept their usual appearance even after their shape had become greatly distorted by the irregular traction of the fibrous tissue. The latter was mostly restricted to areas which had undergone cystic degeneration. Sometimes the bands also spread around lobules, but intersection of these was rare.

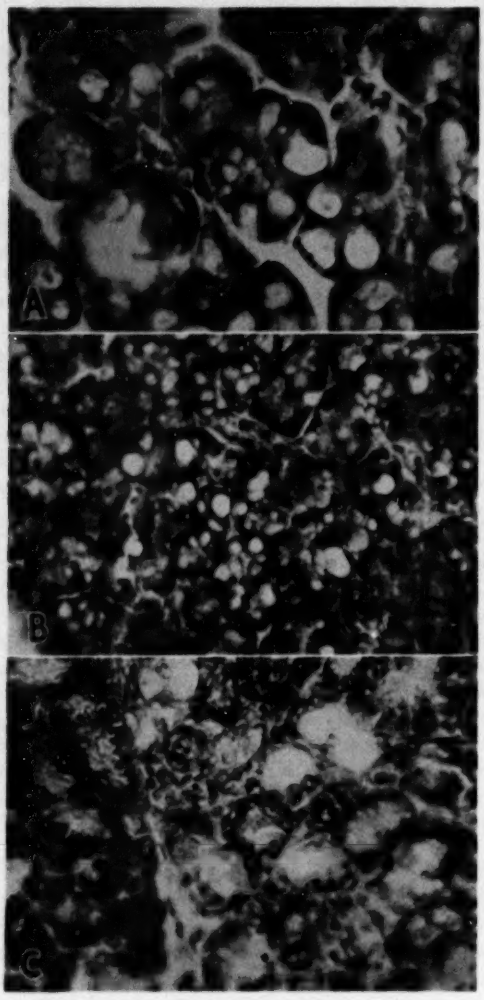


Fig. 2.—*A*, pancreas from rat killed on eighteenth day. Carbon tetrachloride 0.04 Gm. per hundred grams of body weight. Eosinophilia and vacuolation of cells are shown. Hematoxylin and eosin stain; Zeiss apochromatic lens, 4.3 mm. *B*, pancreas from rat killed on tenth day. Carbon tetrachloride 0.07 Gm. per hundred grams of body weight. Diffuse eosinophilia and vacuolation of cells are shown. Hematoxylin and eosin stain; Zeiss apochromatic lens, 8 mm. *C*, pancreas from rat killed on twenty-fifth day. Carbon tetrachloride 0.07 Gm. per hundred grams of body weight. Eosinophilia, vacuolation and dilatation of acini are shown. Hematoxylin and eosin stain; Zeiss apochromatic lens, 4.3 mm.

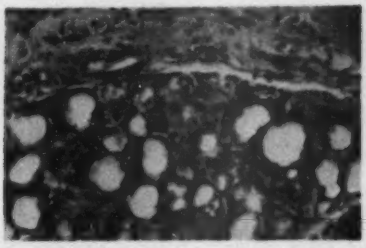

Fig. 3.—Pancreas from rat which died on thirty-fifth day. Carbon tetrachloride 0.07 Gm. per hundred grams of body weight. Dissociation (upper part) and cystic change (lower part) are shown. Hematoxylin and eosin stain; Zeiss apochromatic lens, 8 mm.

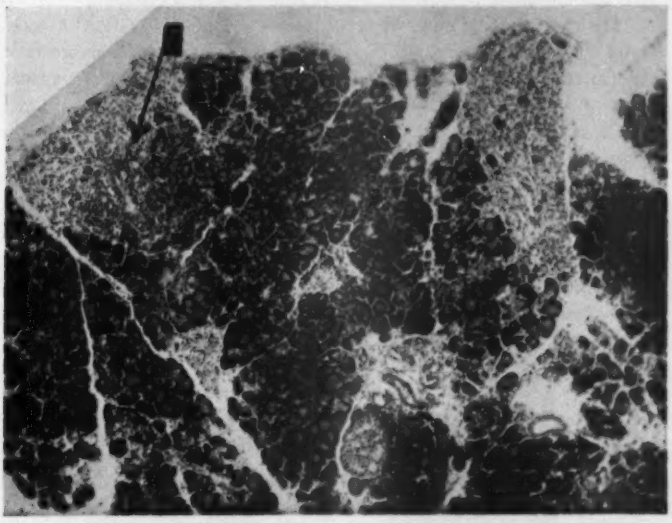

Fig. 4.—Pancreas from rat which died on forty-second day. Carbon tetrachloride 0.07 Gm. per hundred grams of body weight. Dilated acini and ductules are well discernible in left and right upper and left lower quadrants. Coarse eosinophilic granulation and vacuolation are seen in several neighboring cells. Isolated surviving cells are embedded in connective tissue in right upper quadrant. Normal islets of Langerhans are seen in the center and bottom of picture.

A notable exception to the preceding statements was observed in several specimens. In these the eosinophilia and vacuolation did not occur in patches but were uniformly distributed throughout the whole parenchyma from the beginning. With time some solitary cysts were formed and more and more acini became eosinophilic until extensive portions of the parenchyma had undergone degeneration (fig. 6*B*). The process in most acini, however, did not proceed further than vacuolation, and so the cystlike degeneration was by no means general and affected only every tenth to twentieth acinus. The final outcome of the general eosinophilia and vacuolation described is unknown. The character of the process was still unchanged on the one hundred and fiftieth day, when the last animal exhibiting those changes died.

A certain amount of inspissated secretion could be seen in some dilated acini (fig. 5*A*), but the amount was never sufficient to cause obstruction of the ducts. Concrement formation was recorded several times (fig. 6*C*). The intercalated ducts were often dilated in areas which had undergone cystic degeneration, but larger ducts were never affected; metaplasia of the epithelium was not observed.

The characteristic changes induced by daily administration of doses above 0.07 Gm. per hundred grams of body weight were dissociation of the glandular tissue and necrosis. Either of the two forms might appear alone or associated with other changes.

Dissociation of the parenchyma, or at least its earliest stages, might occasionally appear after only a few days of poisoning. First the cytoplasm began to shrink and the acini lost their normal shape, becoming cornered and separated from one another. With time the nuclei also underwent changes such as pyknosis and karyolysis. Finally the gland tissue entirely lost its acinar character; its pancreatic character was hardly recognizable, the parenchyma consisting of nothing else but some fibroblasts and a maze of intercalated ductules surrounding apparently normal islets of Langerhans (figs. 5*B* and 6*A*). Signs of inflammation were sometimes present.

At the beginning of the process of dissociation only a few lobules were affected. In the late stage the entire parenchyma might be involved, but differences in the seriousness of the involvement of various lobules always remained discernible.

Necrosis, while extremely rare following small doses, regularly appeared after amounts of carbon tetrachloride exceeding 0.1 Gm. per hundred grams of body weight had been given for more than a week. The lesion was always focal but might involve extensive portions of the parenchyma. Sometimes several entire lobules were affected while their surroundings remained apparently normal. In fresh necrosis there were always signs of lively regeneration, with simultaneous appearance of fibroblasts (fig. 6*B*). In the late stage nothing but connective tissue

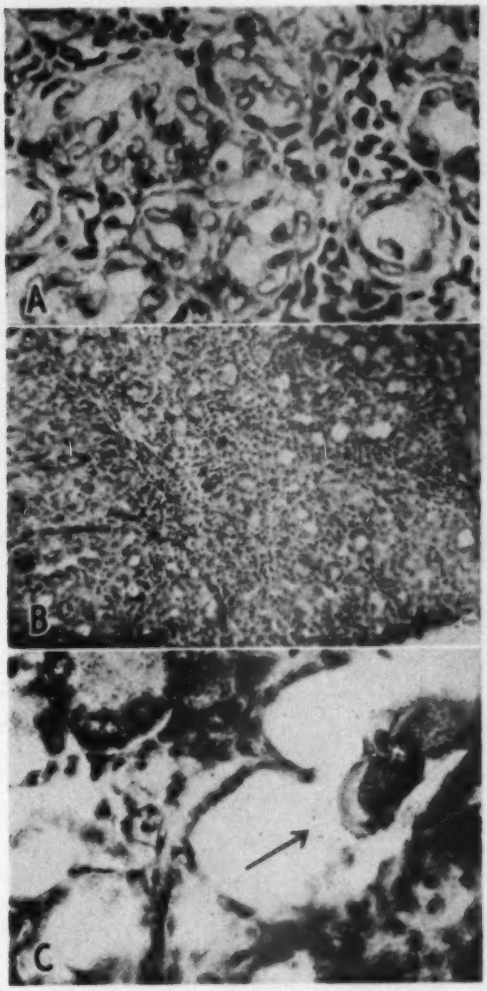


Fig. 5.—*A*, same as figure 8. High power view of part is indicated by the arrow. Zeiss apochromatic lens, 4.3 mm. *B*, pancreas from rat which died on eightieth day. Carbon tetrachloride 0.07 Gm. per hundred grams of body weight. Uniformly distributed vacuolation and cyst formation are seen, as are dissociation, inflammation and beginning of fibrosis. Hematoxylin and eosin stain; Zeiss apochromatic lens, 4.3 mm. *C*, pancreas from rat which died on eighty-fifth day. Carbon tetrachloride 0.07 Gm. per hundred grams of body weight. Concrement formation in dilated cyst is shown. Hematoxylin and eosin stain; Zeiss apochromatic lens, 4.3 mm.

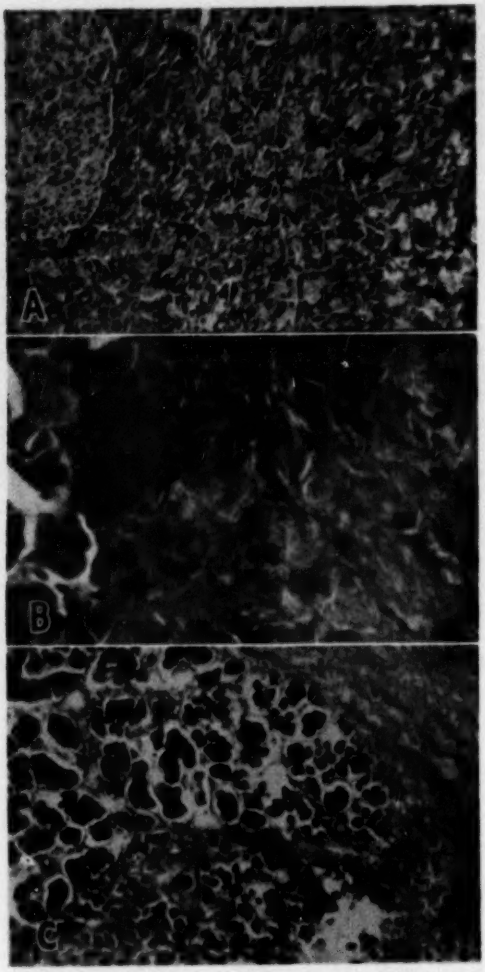


Fig. 6.—*A*, pancreas from rat which died on eighty-fifth day. Carbon tetrachloride 0.07 Gm. per hundred grams of body weight. Concrement formation in dilated cyst is shown. Hematoxylin and eosin stain; Zeiss apochromatic lens, 4.3 mm. *B*, pancreas from rat which died on tenth day. Carbon tetrachloride 1.0 Gm. per hundred grams of body weight. Necrotic area with signs of regeneration and some fibrosis is shown. Hematoxylin and eosin stain; Zeiss apochromatic lens, 4.3 mm. *C*, pancreas from rat which died on fourteenth day. Carbon tetrachloride 1.0 Gm. per hundred grams of body weight. Dissociation and atrophy of acini and fibrosis are shown. Hematoxylin and eosin stain; Zeiss apochromatic lens, 8 mm.

could be discerned at the affected but unregenerated areas, with a few surviving and some totally atrophic acinar cells lying isolated among the fibers (fig. 6*C*). The final outcome was a shrunken scar in which at times remnants of distorted islets were visible.

There was almost no difference in severity between the necrosis produced by a small or by a large amount of the poison beyond a certain minimum; neither did the variation in the quantity administered have an appreciable effect on the duration of recovery.

The extraordinary healing ability of the pancreas was well illustrated by some further observations. According to our experience it took nine days before daily doses of 1.5 Gm. of carbon tetrachloride per hundred grams of body weight killed rats of the strain used in the present experiments. Doses of this size had been administered for three days only and the animals were then killed at various intervals. In those killed on the fourth day frank necroses of the parenchyma were apparent in every instance. After a week a process of active regeneration, starting from the vicinity of the affected areas, characterized the picture; formation of connective tissue was not marked except in extensive necrotic foci. After four weeks the organ showed almost no traces of preceding lesions except some scar tissue situated between apparently intact lobules.

In the lungs peribronchitis and changes of the bronchial wall leading to dilatation of the bronchi in extensive areas were regularly observed. These were reported in detail in another study.[7]

## COMMENT

Our observations on human patients [8] had suggested that lesions of the pancreas occur much more frequently than has been supposed. It was surprising, however, to realize with what regularity pancreatic damage could be induced and how sensitive this organ was to different toxic substances. The observation that quite grave lesions regularly disappear within a short time after discontinuation of the poisoning may account for the fact that pancreatic disease is so rarely diagnosed.

In contrast with the common belief, it was uniformly found that pancreatic lesions preceded lesions of the liver. The greater sensitivity of the pancreas is also shown by the difference in the minimal toxic doses. While 0.07 Gm. of carbon tetrachloride per hundred grams of body weight was sufficient to induce pancreatic lesions, about 0.16 Gm. per hundred grams of body weight has been reported [9] to be necessary to

7. Véghelyi, P. C.; Kemény, T. T., and Sós, J.: Bronchial Changes in Experimentally Induced Cystic Degeneration of the Pancreas, Am. J. Dis. Child. **79**:846 (May) 1950.

8. Véghelyi, P. V.: Secondary Pancreatitis, Am. J. Dis. Child. **74**:45 (July) 1947. Footnote 5 *a*.

9. Cameron, G. R., and Karunaratne, W. A. E.: Carbon Tetrachloride Cirrhosis in Relation to Liver Regeneration, J. Path. & Bact. **42**:1, 1936.

produce minimal hepatic damage, and the minimal amount indicated by the present experiments was also above 0.1 Gm. per hundred grams of body weight. The findings seem to confirm strongly the observations on human subjects [8] that in persons with chronic relapsing pancreatitis disease of the biliary tract may be secondary to the pancreatic disease.

Of the changes observed, necroses seemed to be typical of massive poisoning, just as in human cases, in which this type of lesion is commonly associated with fulminating acute disease. The tendency of pancreatic necroses toward quick restitution without extensive scars, on the one hand, and the strikingly early and grave cirrhoses supervening on chronic dietary lesions,[10] on the other, may perhaps explain the paradox observed by one of us [11] that, whereas in deficiency states of purely nutritional origin enzymatic dysfunction could hardly be restored and most of the infants died, similar states of equally severe clinical appearance due partly to infectious disease showed a much more favorable recovery rate.

Except necrosis, all the changes produced, whether dissociation of the parenchyma, vacuolation or cyst formation with fibrosis, were strikingly similar to those experimentally induced by means of certain diets or observed in infants deficiently nourished.[12] No dietetic factor was responsible for the changes produced in the present experiments, certainly not a vitamin deficiency, especially of vitamin A.

There are several points which need elucidation in regard to the cystic picture, probably the most important of the changes produced. First, the exact pathogenesis remains a problem. No explanation can be given for the common response to both a deficiency in sulfurated amino acids and various toxins. The role of obstruction by inspissated secretion must be rejected not only because obstructed ducts were never found and there were many instances in which no secretion could be detected in the cysts but also because it was always in the farthest portion of the acini where the process of dilation began and the involvement of the ductules seemed to be secondary. Second, it is not known why in animals of the same breed, belonging to the same experimental series, the process of vacuolation or cyst formation is sometimes confined to certain small areas whereas in other animals it affects the whole parenchyma uniformly. Some cases, as for instance that illustrated in figure 3, may

10. Véghelyi, P. V.; Kemény, T. T.; Pozsonyi, J., and Sós, J.: Dietary Lesions of the Pancreas, Am. J. Dis. Child. **79**:658 (April) 1950.

11. Véghelyi, P. V.: Nutritional Edema, Ann. paediat., to be published.

12. Waterlow, J. C.: Fatty Liver Disease in Infants in the British West Indies, Special Report Series, no. 263, London, His Majesty's Stationery Office, 1948. Hartz, P. H.: Pancreatic Atrophy in Infants with Fatty Liver, Documenta Neerl. et Indonesia de Morbis Trop. **1**:41, 1949. Véghelyi, Kemény, Pozsonyi and Sós.[10]

point to differences in blood supply to various parts of the pancreas. It has been ascertained that both hypoxemia and the type of diet fed may play a decisive role in similar effects. Third, there is still no answer to the question why dilatation of acini is seemingly retarded, or in some instances even inhibited, if eosinophilic degeneration and vacuolation of the gland cells is not confined to certain areas.

The picture presented by the cystic change, especially if associated with interacinar fibrosis (fig. 5 *A*), may be strikingly similar to that of cystic fibrosis of the pancreas. The present experiments seem to indicate that a detailed scrutiny is necessary to determine whether toxic factors are or are not involved in the genesis of that disease, particularly since pulmonary changes closely corresponding to those associated with cystic fibrosis may likewise be produced by means of both toxins and diets. Cystic changes exactly similar to those described above may also be induced by chronic administration of metal, for example, zinc and salts. These will be reported in detail in another paper.

SUMMARY

Dilatation of the acini, dissociation of the parenchyma, necroses and subsequent fibrosis were observed in the pancreas of infants dying of dysentery and infantile diarrhea. Similar lesions could be produced in rats by both paradysentery toxin and carbon tetrachloride. The similarity of the changes to those induced by dietetic means and their possible relation to fibrocystic disease of the pancreas is discussed.

Bókay János—Utca 53 (VIII).

Dr. J. Baló assisted in the microscopic diagnosis.

# PRIMARY SARCOMA OF LIVER

## Report of a Case

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AND
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PRIMARY sarcoma of the liver is rare. There is confusion in the classification of these neoplasms, and this is due in part to the histologic similarity between a highly anaplastic carcinoma and a sarcoma. This classification difficulty is encountered also because the exact origin of many of these tumors is uncertain, that is, extension to the liver from the adrenal glands, diaphragm, thoracic wall, etc. For these reasons, an accurate account of the reported cases of primary sarcoma of the liver is unreliable; Shallow and Wagner [1] estimated that 100 authentic cases have been reported.

The true source of mesodermal neoplasms has never actually been traced, although various opinions have been voiced in the literature.[2] Many of these thoughts have been discussed in the review of Shallow and Wagner.[1] Jaffe [3] found that 29 per cent of his series of patients with hepatic sarcomas had a concomitant cirrhosis. Franklin and Downing,[4] in attempting to explain the pathogenesis of all primary liver tumors, emphasized the process of regeneration in damaged liver tissue and in part blamed an abnormal regenerative hyperplasia for the neoplastic transformation. Goldstein,[5] in his study of 11 pediatric cases, stated that primary sarcoma of the liver is a rare entity and all cases should be reported.

### REPORT OF CASE

J. H., a 6 year old white girl, in March 1949 had the chief complaint of pain of two months' duration in the upper part of the abdomen. Accompanying this vague

From the Department of Pathology, University of Texas School of Medicine.

1. Shallow, T. A., and Wagner, F. B.: Primary Fibrosarcoma of the Liver, Ann. Surg. **125**:439 (April) 1947.

2. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 752.

3. Jaffe, R. H.: Sarcoma and Carcinoma of the Liver Following Cirrhosis, Arch. Int. Med. **33**:330 (March) 1924.

4. Franklin, R. G., and Downing, C. F.: Primary Liver Tumors, Am. J. Surg. **73**:390, 1947.

5. Goldstein, H. I.: Primary Sarcoma of the Liver, Internat. Clin. **2**:73, 1921.

abdominal pain was a history of persistent septic temperature elevation of 102 to 103 F. She was hospitalized in April by her local physician, who found tenderness in the right upper abdominal quadrant with rigidity and hepatomegaly. Results of complete laboratory and roentgen studies were either normal or negative.

The patient failed to respond to multiple antibiotic therapy, and on April 30 an exploratory laparotomy was performed. Multiple aspirations of the liver revealed clear fluid which proved sterile on culture. The remaining history was not significant.

Fig. 1.—Section of the liver showing encapsulation of the tumor with areas of necrosis and degeneration.

On admission to this hospital in June, the physical examination revealed a chronically and acutely ill girl. The chest was asymmetric, with fulness and splinting of the right side along with dulness to percussion in the right lower part of the chest. A small draining sinus was still present in the abdominal operative wound. The liver was enlarged 5 cm. downward and to the left of the midline. Some rigidity and a definite tenderness were present in the right upper abdominal quadrant.

Significant laboratory studies showed a red blood cell count of 2,500,000, and a hemoglobin content of 6.4 Gm. per 100 cc. The white blood cell count was 30,300,

with a shift to the left. Bone marrow studies revealed normal cellularity. A routine flat roentgenogram of the abdomen showed an elevation of the right hemidiaphragm. Intravenous pyelograms and oral cholecystograms showed no abnormalities and examination of the liver with thorium dioxide (thorotrast®) was unsuccessful.

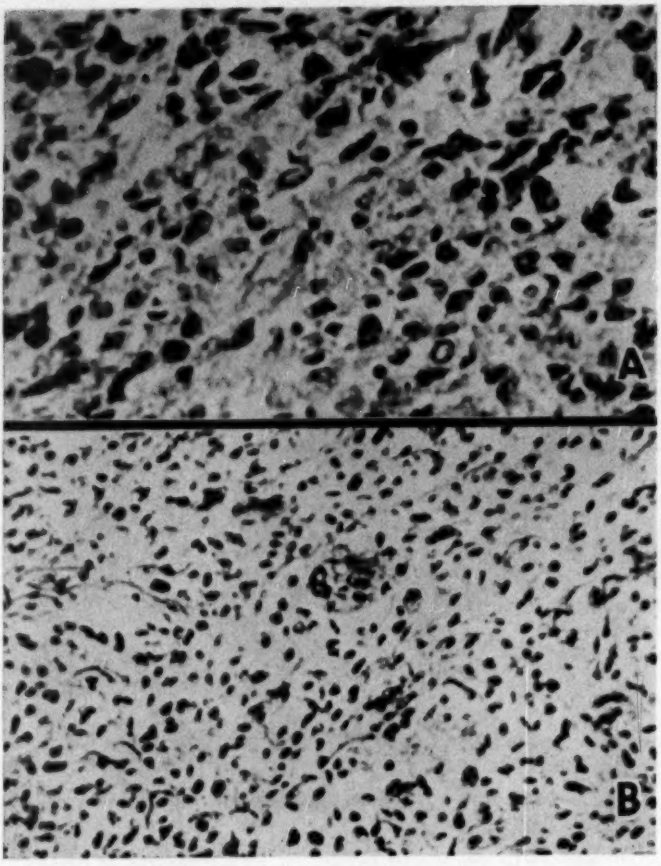


Fig. 2.—*A*, microscopic section through the hepatic tumor mass showing variation in the cellular outline and chromatism. Hematoxylin and phloxine; × 725. *B*, section of the hepatic sarcoma revealing the distribution of reticulum. Wilder's stain; × 475.

The hospital course was one of spiking fever, with a progressive downhill course. Various diagnostic studies were constantly done in an effort to arrive at a positive diagnosis. Blood transfusions temporarily improved the status of the

patient. On July 8, another exploratory laparotomy was performed, and biopsy of the mass in the right upper abdominal quadrant was reported as a sarcoma.

Postoperatively, the patient continued her steady regression and died on July 22.

*Autopsy Findings.*—An autopsy was performed 10 hours after death, and the pertinent changes were in the abdomen. The right lobe of the liver was markedly enlarged with a fibrous capsular adhesion to the hepatic flexure of the colon. After removal, the liver weighed 3,750 Gm. (normal, 642 Gm.) and on sectioning showed a round 15 cm. mass occupying the greatest portion of the right lobe. This mass was well delimited by a fibrous capsule and showed many areas of cystic degeneration, necrosis and hemorrhage (fig. 1).

Microscopic examination of the tumor showed a marked variation in the cellularity, in many areas the cells being closely packed while in other portions there was a loose arrangement (fig. 2*A*). The individual cells varied from spindle to polyhedral in shape, many being small and hyperchromatic. Numerous neoplastic and foreign body giant cells were noted. Special stains revealed a uniform distribution of reticulum fibers characteristic of a sarcoma (fig. 2*B*). A microscopic section through the hepatic flexure of the colon showed an inflammatory reaction with encroachment of the neoplasm on the serosa.

No malignant growth was found elsewhere in the body. The final anatomic diagnoses were (1) primary undifferentiated sarcoma of the liver, with extension to the serosa of the hepatic flexure of the colon; (2) hydroperitoneum, (200 cc. of fluid) and (3) hydrothorax on the right (300 cc. of fluid).

## SUMMARY

A brief review of the literature concerning primary sarcoma of the liver is presented.

A case of primary undifferentiated sarcoma of the liver with a complete autopsy is reported.

# PULMONARY TOXICITY OF WETTING AGENTS DISPENSED AS AEROSOLS

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IN THE last few years several investigators have employed the so-called wetting agents in various fields pertaining to medicine. Among the many uses, the following may be mentioned: (1) as agents to increase fat absorption in patients with pancreatic fibrosis, (2) as mucigogic agents in the treatment of peptic ulcers, (3) as ingredients of dentrifices, (4) as solvents for penicillin aerosols, (5) as agents used to wet down dusts in mines, (6) as substances used in combination with sulfonamides to increase penetration of the drugs through the cornea and (7) as agents to increase the moisture in croup tents in treatment of children with laryngotracheobronchitis and similar diseases.

Previous experimental work concerning the toxicity of these agents was limited to observation of the effects following oral, intravenous and intraperitoneal administration. Gershenfeld and Witlin [1] investigated thoroughly the toxicity in rabbits of a large number of wetting agents. They observed no evidence of toxicity as determined by following the red blood cell count, the leukocyte count, the hemoglobin level and the differential smear. They also followed the weight curve, appetite and activity. However, these authors employed the oral, intravenous and intraperitoneal routes of administration and not the respiratory route. Furthermore, they did not study the animals histologically. In view of the fact that there is considerable interest in the use of wetting agents by aerosol administration, it was decided to study the toxicity of various such agents in the respiratory tract.

Morris [2] gave an excellent chemical review of these agents from the medical viewpoint. Briefly, these compounds contain two radicals: (1)

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From the Department of Pharmacology, University of Virginia, Department of Medicine.

This investigation was supported in part by a research grant from the Federal Security Agency, United States Public Health Service, National Institutes of Health.

1. Gershenfeld, L., and Witlin, B.: Surface Tension Reducents in Bactericidal Solutions: Their in Vitro and in Vivo Efficiencies, Am. J. Pharm. **113**:215 (June) 1941.

2. Morris, G. E.: Brief Review of Chemistry of Wetting Agents, J. Indust. Hyg. & Toxicol. **26**:175 (May) 1944.

a long hydrocarbon chain, which is the lipophilic or hydrophobic group and (2) a short -$SO_4Na$ group, which is the lipophobic or hydrophilic group. Therefore, when these agents are dissolved in water, the hydrophilic group is alined on the surface next to the water, and the lipophilic group is directed upward toward the overlying gas. Consequently, the surface now has a film which is oil-like and has a much lower surface tension than water alone.

## METHODS

The various wetting agents were selected on the basis of stability in aqueous solution, absence of excessive soapiness and absence of objectionable odor (table 1).

Guinea pigs weighing an average of 400 Gm. were used. These animals were put into conventional aerosol chambers. A flowmeter was attached to insure that each animal received approximately the same amount of aerosol. There was a constant inflow and outflow of the agent. The various wetting agents were dispensed in concentrations of 1.0, 0.5 and 0.1 per cent, and atmospheric air was used to convert the solution to aerosol. The animals were exposed in this fashion for eight

TABLE 1.—*Wetting Agents Used and Their Manufacturers*

| | Product | Type | Manufacturer |
|---|---|---|---|
| (1) | Duponol C* | Sodium lauryl sulfate | E. I. duPont de Nemours and Company |
| (2) | Aerosol OS* | Alkylaryl sulfonate | American Cyanamid Company |
| (3) | Tergitol 08* | Synthetic primary alcohol sulfate | Union Carbide and Carbon Corporation |
| (4) | Aerosol MA* | Sulfonated ester of dicarboxylic acid | American Cyanamid Company |

* Registered trademark.

hours a day for six days. At the end of a week those not already dead were killed by a blow on the head or with amobarbital sodium (amytal sodium®) and studied by autopsy. Histologic sections were made of the trachea, bronchi and lungs.

## RESULTS

In every case the degree of dyspnea exhibited by the animals was proportional to the concentration of the wetting agent received. All the animals receiving 1 per cent concentrations were markedly dyspneic. Those receiving 0.5 per cent concentrations were mildly to moderately dyspneic, and those receiving 0.1 per cent concentrations at no time exhibited dyspnea. Animals in the control test, run simultaneously with use of water alone, at no time exhibited dyspnea. Three of every four animals receiving sodium lauryl sulfate (duponol C®) in 1 per cent concentration died in a short time. None of the animals receiving the other agents in 1 per cent concentration died, but they were all rather dyspneic and lethargic. None of the animals receiving 0.5 or 0.1 per cent concentration of any agent died. The onset of dyspnea was rapid, taking place in one to three hours after exposure. A total of 50 animals was used; the results are shown in table 2.

TABLE 2.—*Concentrations of Wetting Agents and Results of Experiment*

| | Concentration of Wetting Agent | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Duponol C* | | | Aerosol OS* | | | Aerosol MA* | | | Tergitol 08* | | |
| | 0.1% | 0.5% | 1.0% | 0.1% | 0.5% | 1.0% | 0.1% | 0.5% | 1.0% | 0.1% | 0.5% | 1.0% |
| Number of animals | 4 | 4 | 6 | 4 | 4 | 4 | 4 | 4 | 4 | 2 | 2 | 2 |
| Number of deaths | 0 | 0 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Degree of dyspnea | 0 | 2+ | 4+ | 0 | 2+ | 4+ | 0 | 2+ | 4+ | 0 | 1+ | 2+ |

* Registered trademark.

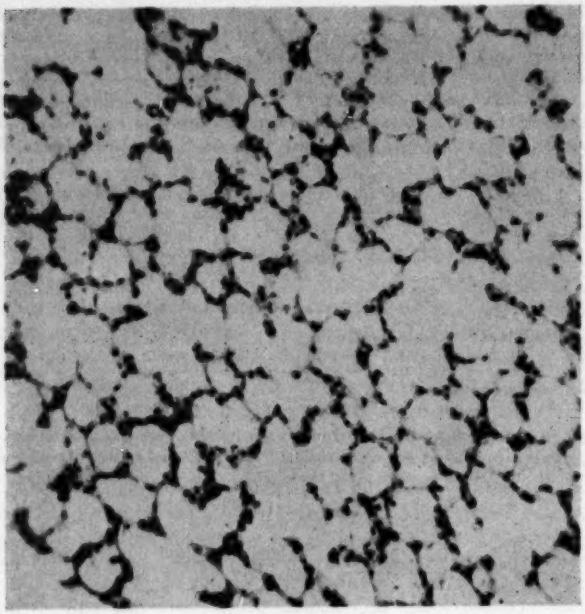

Fig. 1.—Absence of change in the lung of animal receiving 0.1 per cent concentration of sodium lauryl sulfate.

The only change noted on gross examination at autopsy was increase in the size and firmness of the lungs of the animals which received 1 per cent concentrations of the agents. However, on histologic section the changes were marked, the degree of change depending on the concentration received. The lungs of those receiving 1 per cent concentration exhibited a widespread reaction characterized by outpouring of polymorphonuclear cells and macrophages, proliferation of fibroblasts of septal walls, degeneration and desquamation of pulmonary epithelium and proliferation of alveolar epithelium. Large areas of alveoli were

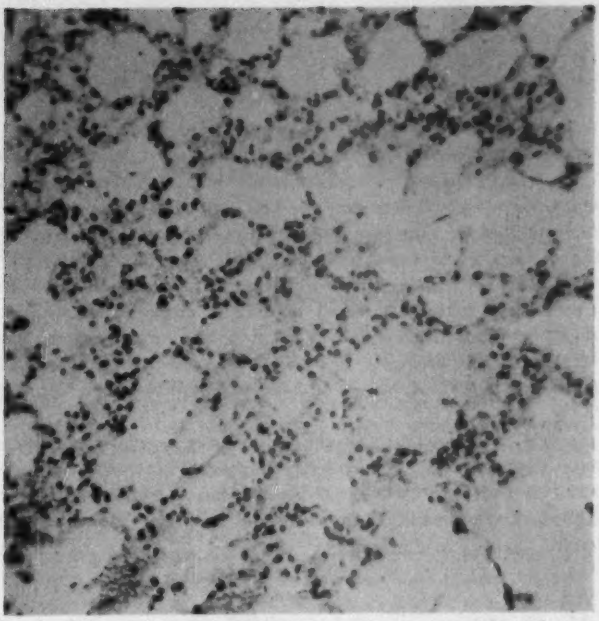

Fig. 2.—Only minimal changes in the lung of animal receiving 0.5 per cent concentration of sodium lauryl sulfate.

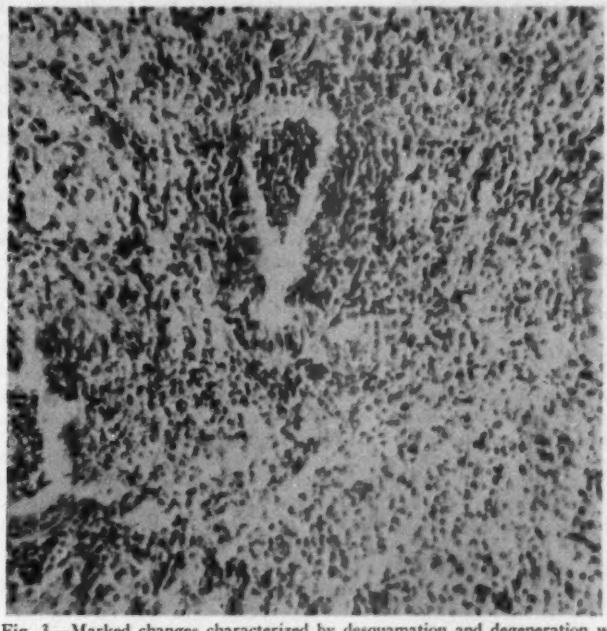

Fig. 3.—Marked changes characterized by desquamation and degeneration with secondary proliferation in animal receiving 1.0 per cent concentration of sodium lauryl sulfate.

completely obliterated by this reaction. Those animals receiving 0.5 per cent concentration exhibited a mild reaction. Animals receiving 0.1 per cent concentration and control animals did not exhibit these changes. The changes were only minimal with synthetic primary alcohol sulfate (tergitol 08*), even in 1 per cent concentration. These histologic changes seem to be consistent with those described by Ross.[3] He showed that by injecting various irritating and toxic agents intratracheally into rabbits he could produce a change characterized by proliferation of alveolar epithelium and invasion of macrophages. Therefore, the reaction seems to be one of response to irritation. These changes are illustrated by the accompanying photomicrographs (figs. 1 to 3).

Several of the animals that did not die after receiving sodium lauryl sulfate (duponol C*) and alkylaryl sulfonate (aerosol OS*) were allowed to live for two months. At the end of two months they all exhibited extreme inanition, anorexia and lassitude. There were characteristic changes in the lungs.

## SUMMARY

The effects of several well known wetting agents on the respiratory tract of guinea pigs were investigated. It was noted that these agents were toxic in proportion to their concentration. This toxicity consisted in degeneration and desquamation of alveolar epithelium and invasion of alveolar spaces by macrophages, with subsequent proliferation of fibroblasts and alveolar epithelium. In 0.1 per cent concentration the agents are apparently nontoxic to guinea pigs. From this study it would seem advisable to limit the concentration of wetting agents to 0.1 per cent in experimental investigation in man.

Dr. C. L. Gemmill and Dr. D. T. Watts gave advice and helpful criticism. The Vaponefrin Company supplied the nebulizers used in this work, and the following companies supplied the wetting agents: E. I. duPont de Nemours and Company, American Cyanamid Company and Union Carbide and Carbon Corporation.

The clinical investigation of the use of wetting agents in the treatment of laryngotracheobronchitis is now being carried out by Dr. F. W. Regnier, of the Department of Otolaryngology of the University of Virginia Hospital, and will be reported on at a later date.

3. Ross, I. S.: Pulmonary Epithelium and Proliferative Reactions in Lungs: Study of Cellular Response in Lungs After Intratracheal Injection of Toxic and Nontoxic Foreign Substances, Arch. Path. **27**:478 (March) 1939.

# Case Reports

## ACUTE SUPPURATIVE INFECTIONS OF THE SALIVARY GLANDS IN THE NEWBORN

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Acute suppurative infection of the salivary glands, or sialadenitis, is a distinct entity and occurs not infrequently during the first four weeks of life. The clinical syndrome is characterized by swelling of the gland, fever, anorexia, irritability and failure to gain weight. The ultimate diagnostic criterion is the appearance of pus in the oral cavity exuding from the natural opening of the involved salivary gland on gentle external pressure over the gland. Usually a single gland is involved, oftenest the parotid, although all the salivary glands have been reported to be affected.

I am reporting 2 cases of acute infection of a salivary gland occurring in the neonatal period. In the first case the left parotid gland was the seat of the infection, and in the second the right submaxillary gland was involved.

### REPORT OF CASES

CASE 1.—Baby S. M., a white female infant, was delivered by cesarean section. She weighed 6 pounds 4 ounces (2,838 Gm.) and measured 20 inches (50.8 cm.) in length. There was no difficulty in establishing respiration, and no application of suction to the mouth was necessary. The infant was immediately taken to the nursery and placed in an incubator as part of the usual nursery routine. Physical examination in the nursery revealed a normal infant. At twelve hours administration of an evaporated milk formula was started. During the first two days the infant lost 2½ ounces (71 Gm.) but otherwise appeared normal. On the third day the infant weighed 6 pounds 3 ounces (2,810 Gm.) and remained at that weight. On the seventh day the temperature rose to 102.4 F. Examination revealed a large tense swelling over the left parotid gland, with the overlying skin appearing taut and shiny. Intraoral examination showed pus exuding from the orifice of Stensen's duct on the left following gentle external pressure. Examination of the pus showed many polymorphonuclear leukocytes and gram-positive cocci. Culture of the purulent material was subsequently reported positive for hemolytic Staphylococcus aureus.

The patient was transferred to the children's ward, and penicillin therapy was started. An initial dose of 50,000 units was given intramuscularly, followed by 25,000 units every three hours. A hypodermoclysis of 50 cc. of 2.5 per cent glucose solution in saline solution was given, and warm water compresses were applied at regular intervals to the swollen area. A blood count done on the patient's admission to the children's ward showed a hemoglobin concentration of 15.4 Gm. per hundred cubic centimeters and a red blood cell count of 5,020,000 and a white blood cell count of 23,200 per cubic millimeter. The differential count showed 41 per cent polymorphonuclear forms, 51 per cent lymphocytes, 2 per cent monocytes and 6 per cent eosinophils. The temperature returned to normal

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three days after penicillin therapy was begun, and the white blood cell count fell to 10,750 per cubic millimeter, with 42 per cent polymorphonuclear cells, 53 per cent lymphocytes, 3 per cent monocytes and 2 per cent eosinophils. The swelling had completely subsided, and therapy was discontinued five days after the onset of the infection. The infant took her feedings well and at her discharge, one week after the initial swelling, weighed 6 pounds 8 ounces (2,951 Gm.).

Case 2.—Baby V. J., a 3 week old Negro boy, was admitted to the hospital because of a swelling on the right side of the jaw. No other symptoms were present. There was no history of maternal sepsis. On his admisison the temperature was 100.6 F. On examination a small nonfluctuant swelling was seen under the right side of the mandible, and gentle pressure exerted over this area produced thick yellow pus from the orifice of the right submaxillary gland within the mouth. Culture of this material yielded hemolytic Staph. aureus. An initial blood count showed 24,600 white blood cells per cubic millimeter, with 82 per cent polymorphonuclear forms, 16 per cent lymphocytes and 2 per cent monocytes. The hemoglobin content was 16.5 Gm. per hundred cubic centimeters, and the red blood cell count was 5,100,000 per cubic millimeter.

Penicillin therapy was begun on his admission, with an initial dose of 20,000 units intramuscularly and a similar dose every three hours thereafter. After two days the temperature was normal. The submaxillary swelling subsided on the fourth day and was scarcely palpable on his discharge. Administration of penicillin was continued until the seventh day. The infant's weight had increased from 4 pounds 12 ounces (2,152 Gm.) on his admission to 5 pounds 5 ounces (2,417 Gm.) at his discharge from the hospital on the eighth day.

## PATHOGENETIC ASPECTS

The pathogenesis of this acute suppurative process is usually not apparent; it may occur by more than one route. The two most likely avenues of onset are (*a*) an ascending infection from within the oral cavity to the affected gland via the secretory duct and (*b*) a hematogenous metastatic infection.

The ascending mode of infection may occur in suckling when there is fissuring or infection of the nipple. Local trauma to the mouth may also prepare the way for retrograde infection. Baxter and Mac Donald[1] suggested such a mechanism in their report of a case of acute suppurative parotitis after a brow presentation with pronounced edema of the face and eyelids. They suggested that the parotitis is secondary to the face presentation or to the trauma to Stensen's duct in the process of forcible wiping of the mouth when it presents during the delivery. Removal of mucus from the mouth with a gauze-covered finger is not an uncommon practice and may inadvertently traumatize the ductal openings, with subsequent retrograde infection. It is also possible that the overzealous use of suction apparatus may injure the oral mucosa and prepare the way for infection. Bacterial invasion via a contaminated rubber nipple is possible. Likewise, extension from a nearby infection, as otitis media, may be the method of onset.

The hematogenous pathway infers a septicemia with a metastatic focus in the involved gland. Maternal sepsis may account for the focus, with placental transmission and ultimate localization. A primary cutaneous infection may provide the nidus for later infection of the blood stream and metastases. Oftener than not, the primary focus remains obscure. The absence of a demonstrable portal of entry does not exclude the possibility of a blood stream infection. Waddell, Balsley and

1. Baxter, R. H., and Mac Donald, M. T.: Acute Suppurative Parotitis in the Newborn, New England J. Med. **217**:351 (Aug. 26) 1937.

Grossman,[2] in taking blood cultures from 34 newborn infants to explain the cause of anorexia, listlessness and loss of weight, recovered hemolytic Staphylococcus, usually of the albus variety, in 64.7 per cent of their series. Such a recovery rate seemed too high to be accounted for by contamination of the skin and appeared to be significantly related to the symptom complex they investigated. Silverman and Homan,[3] in reviewing the subject of sepsis of obscure origin in the newborn, discussed those cases in which the origin of the septicemia is not clinically apparent and in which metastatic involvement, usually of the visceral type, is a secondary phenomenon. Their series consisted of 25 cases of sepsis during the first month of life, collected over an eleven year span at the Babies Hospital, in New York. In each of their cases the infection of the blood stream was considered to be the major disturbance and the visceral involvement secondary. Such an explanation can account for the appearance of acute suppurative sialadenitis in a newborn infant without a demonstrable focus of infection or oral lesion.

## RESULTS OF BACTERIOLOGIC STUDIES

The organism most frequently recovered in cases of acute infection of a salivary gland reported in the literature is the hemolytic Staphylococcus. Sanford and Shmigelsky [4] reported 5 cases of parotitis all due to hemolytic Staph. aureus. Neuhauser and Ferris [5] reported 4 cases of acute parotitis in infants, all caused by Staph. aureus. The organism recovered by Reisman and Fisher [6] in their case of acute suppurative parotitis in a premature infant was hemolytic Staph. aureus. Elterich,[7] in his comprehensive review of the subject, found staphylococci to be the organisms most frequently cultured from the pus of the affected salivary gland. That other organisms may also cause the same pathologic involvement was shown by the report of Baxter and Mac Donald.[1] They demonstrated streptococci on direct smear from pus taken from Stensen's duct and obtained colon bacilli and Bacillus alkaligenes (Alcaligenes faecalis) in the culture. Cultures in Burke's [8] case yielded both hemolytic Staphylococcus albus and nonhemolytic Streptococcus. Other organisms reported were Oidium (Candida) albicans and diplococci.

## DIAGNOSIS

The diagnosis of acute suppurative disease of one or more of the salivary glands is not difficult in the neonatal period. The characteristic findings of soft tissue swelling, fever, anorexia and pus exuding from the intraoral ductal opening do not occur in other conditions which may offer diagnostic problems. Mumps is rare

2. Waddell, W. W., Jr.; Balsley, R. E., and Grossman, W.: The Significance of Positive Blood Cultures in Newborn Infants, J. Pediat. **33**:426 (Oct.) 1948.

3. Silverman, W. A., and Homan, W. E.: Sepsis of Obscure Origin in the Newborn, Pediatrics **3**:157 (Feb.) 1949.

4. Sanford, H. N., and Shmigelsky, I.: Purulent Parotitis in the Newborn, J. Pediat. **26**:149 (Feb.) 1945.

5. Neuhauser, E., and Ferris, B., Jr.: The Treatment of Acute Suppurative Parotitis in Infants, J. Pediat. **27**:589 (Dec.) 1945.

6. Reisman, H. A., and Fisher, G.: Acute Suppurative Parotitis in Newborn Premature Infants, Am. J. Dis. Child. **71**:387 (April) 1946.

7. Elterich, T. O.: Purulent Parotitis in the Newborn, J. Pediat. **3**:761 (Nov.) 1933.

8. Burke, F. G.: Suppurative Parotitis in an Infant, Clin. Proc. Child. Hosp. **4**:68 (Feb.) 1948.

in the neonatal period, and, although the parotid gland is swollen, it is firm and not associated with the presence of pus in Stensen's duct after application of gentle external pressure. Glaser and his associates [9] reported a case of rare congenital hemangioma of the parotid gland. They stated the characteristic findings are appearance in early life, unilateral occurrence, enlargement of the tumor when the infant cries, elastic consistency and compressibility and evidence of lobulation on palpation. There is no associated fever. Postoperative suppurative parotitis is not a neonatal problem, nor is post-typhoid parotitis.

### THERAPY

As in most acute suppurative conditions, the use of chemotherapeutic and antibiotic agents has altered the treatment and prognosis of suppurative infections of the salivary gland in the newborn period. Prior to the advent of modern therapy, surgical intervention was the ultimate mode of therapy. The principle of incision and drainage was properly applied. The use of local wet dressings and/or roentgen therapy occasionally obviated the surgical procedure but oftener only preceded it. Treatment with sulfonamides alone or in combination with nonspecific therapy has had limited value. Administration of penicillin with sulfadiazine has produced good results. Penicillin alone in adequate dosage has resulted in quick resolution of the infectious process, with prompt recovery. This was vividly shown in the 2 cases herein reported.

### SUMMARY

1. Two cases of acute infection of a salivary gland in the neonatal period treated with penicillin, with recovery, are presented.

2. Pathogenetic aspects, results of bacteriologic studies, diagnosis and treatment are reviewed.

2320 Foster Avenue (10).

9. Glaser, K.; Mehn, W. H., and Schultz, L. W.: Congenital Hemangioma of the Parotid Gland, J. Pediat. **28**:729 (June) 1946.

# CONGENITAL MYELOGENOUS LEUKEMIA

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Medical Corps, Army of the United States
AND
LIEUTENANT COLONEL LEO J. GEPPERT
Medical Corps, United States Army

Leukemia in the newborn is rare and unique in that it is almost invariably of the myelogenous type. Kelsey and Anderson,[1] in a comprehensive survey of the literature up to 1939, collected 17 reported cases of congenital leukemia. Of these, they accepted only 9 as instances of unquestionable congenital leukemia, the remaining 8 cases being probable examples of unsuspected erythroblastosis fetalis or leukemoid responses secondary to infection. Of the 9 verified cases of congenital leukemia, 8 were of the myelogenous type, only 1 being lymphogenous. Kelsey and Anderson reported an additional case of verified congenital myelogenous leukemia. Further reports of cases,[2] all of the myelogenous type, have appeared since. It is of considerable interest that the illness of the infant reported on by Keith,[2e] which died at the age of 16 months, followed a course not unlike that usually seen in older infants with leukemia.

The present case is reported because of the rarity of the disease, because of the unusual cutaneous manifestations and because difficulty was encountered in differentiating the condition from erythroblastosis fetalis.

## REPORT OF A CASE

A white boy,[3] 1 day of age, was admitted on Feb. 20, 1947, to the pediatric section of Brooke General Hospital with the history of skin tumors and blood-streaked vomitus.

The patient was born February 19, delivery being uncomplicated. The weight at birth was 9 pounds (4,082 Gm.). The infant appeared normal at birth except for the presence of multiple purple and blue tumors in the skin. The formula offered at 1 day of age was vomited, the vomitus being streaked liberally with blood. A white blood cell count taken shortly after birth was 208,000.

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From the Pediatric Section, Medical Service, Brooke General Hospital, Fort Sam Houston, Texas.

1. Kelsey, W. M., Jr., and Anderson, D. H.: Congenital Leukemia, Am. J. Dis. Child. **58**:1268 (Dec.) 1939.

2. (*a*) Morrison, M.; Samwick, A. A., and Rubinstein, R. I.: Congenital Leukemia with "Chloroma," Am. J. Dis. Child. **58**:332 (Aug.) 1939. (*b*) Poncher, H. G.; Weir, H. F., and Limarzi, L. R.: Chronic Myelogenous Leukemia in Early Infancy, J. Pediat. **21**:73 (July) 1942. (*c*) Hamne, B.: A Case of Congenital Myeloid Leukemia, Acta pædiat. **31**:330, 1944. (*d*) Cross, F. S.: Congenital Leukemia, J. Pediat. **24**:191 (Feb.) 1944. (*e*) Keith, H. M.: Chronic Myelogenous Leukemia in Infancy, Am. J. Dis. Child. **69**:366 (June) 1945.

3. Dr. Sidney Kaliski, San Antonio, Texas, referred this patient to the Pediatric Section, Brooke General Hospital.

The parents and a 3 year old sibling had been in good health, and there was no family history of blood dyscrasia or chronic infection. The mother's serologic reaction for syphilis was negative.

Physical examination revealed a well developed male infant who did not appear critically ill. The findings of note were confined to the skin and the abdomen. Numerous moderately firm purple and blue tumors were present in the skin and extended into the subcutaneous tissue. They measured 1 to 4.5 cm. in diameter and protruded 0.25 to 1 cm. above the surface of the skin (fig. 1). The largest lesions were surrounded closely by pinhead-sized nodules which were similar to the larger tumors in appearance and consistency. Petechiae were scattered abundantly between the tumors. The abdomen was somewhat protuberant, the liver extending 7 cm. below the right rib margin and across the midline to the left midclavicular line. The spleen was palpable 4 cm. below the left rib margin. Enlargement of lymph nodes was not noted, nor was there any icterus of the scleras or skin.

Fig. 1.—Infant with leukemia cutis.

*Laboratory Findings.*—The hemoglobin concentration on the infant's admission was 94 per cent; red blood cells numbered 4,170,000 and white blood cells 198,000. A smear of peripheral blood (fig. 2) showed predominantly young myeloid cells which were peroxidase positive and an infrequent number of thrombocytes. Bleeding time exceeded fifteen minutes; a clotting time of five minutes and a prothrombin time exceeding five minutes were recorded. Total white blood cell counts during the course in the hospital ranged between 134,500 and 210,000, the predominance of immature cells of the myeloid series remaining unchanged. By the fourth day of life the hemoglobin concentration had decreased to 70 per cent and the red blood cells to 2,930,000.

A biopsy specimen of tibial bone marrow [4] revealed the following percentages of cells: myeloblasts, 6.4; promyelocytes, 59.0; neutrophilic myelocytes, 2.4; basophilic myelocytes, 0.2; neutrophilic metamyelocytes, 0.4; neutrophilic "bands," 0.8;

4. The bone marrow examinations were made by Lieut. Col. H. A. Van Auken, Medical Corps, formerly of the Laboratory Service, Brooke General Hospital.

neutrophilic "filaments," 1.8; eosinophilic "filaments," 0.2; small lymphocytes, 10.4; "smudge cells," 8.2; pronormoblasts, 0.6; basophilic normoblasts, 2.6; acidophilic normoblasts, 6.4, and unidentified cells, 0.6.

On the day of the infant's admission a skin tumor was removed from the abdomen, with the area under local anesthesia, for microscopic examination (fig. 3). Roentgenograms of the long bones and skull showed no abnormal findings. The blood Kahn reaction was negative.

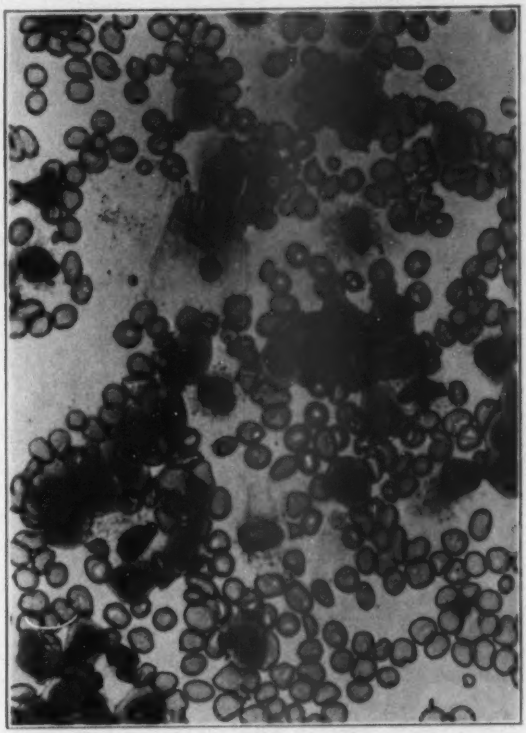

Fig. 2.—Photomicrograph of peripheral blood smear; high power.

Serologic typing of the parents and patient classified the mother as type O, Rh negative; the father as type A, Rh positive, and the patient as type A, Rh positive. Atypical agglutinins, including blocking antibodies, were not demonstrated in the mother's blood serum, and no abnormal agglutinins were found in the patient's blood. The white blood cell counts and morphologic studies on the cells of the parents showed no abnormalities. No bone marrow studies were carried out on the parents.

*Course in the Hospital.*—The patient was given orally a mixture of 5 per cent solution of protein hydrolysates (amigen®) and 5 per cent dextrose solution, which

was vomited after feedings, the vomitus containing fresh blood. On the second day of life (February 21) therapy consisting of 5 cc. of 10 per cent solution of urethane U. S. P. was initiated as a rectal instillation every twelve hours. On the third day of life the infant showed an elevation in temperature ranging between 100 and 102 F. rectally. The therapy employed did not reduce appreciably the white blood cell count, nor did it alter the course of the disease. Two days later the patient appeared unusually lethargic; respirations became shallow and irregular, and he died the same day, the fourth day of life.

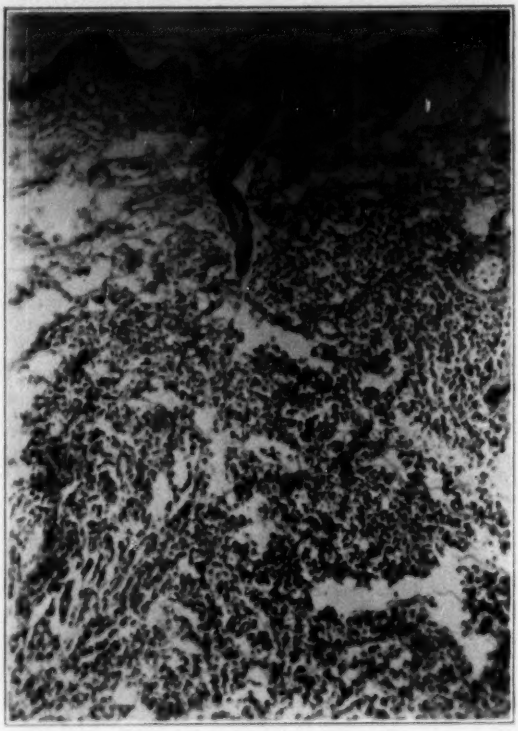

Fig. 3.—Photomicrograph of leukemic infiltrations of the skin; low power.

During the course of the stay in the hospital there was no edema and no jaundice. The liver and spleen increased in size.

*Observations at Autopsy.*[5]—Gross Examination: The body was that of a moderately well nourished infant who presented skin lesions as described in the clinical protocol. A large subarachnoid hemorrhage was observed overlying the left cere-

5. The autopsy was performed by Lieut. Col. Robert H. Holmes, Medical Corps, formerly of the Laboratory Service, Brooke General Hospital.

brum, and a small amount of fresh blood was present in the left lateral ventricle. The liver weighed 300 Gm. (fig. 4) and was mottled with gray-yellow tumors. The spleen, which weighed 37.5 Gm., showed similar gray-yellow infiltrations. The stomach and intestinal contents consisted primarily of clotted blood, and the mucosa was marked by numerous petechiae and scattered gray-yellow nodules. The renal pelves contained punctate hemorrhages. Examination of the heart revealed pale yellow nodules in the epicardium and myocardium. Many small cloudy opacities were noted beneath the pleura of the lungs; cut sections of the lungs were frothy and hemorrhagic.

Microscopic Examination: The appearance of the spleen was divergent in that the malpighian follicles were compressed, and the sinusoids were widened and irregular and were filled with closely packed immature myeloid cells. The architecture of the liver and lymph nodes was obliterated almost completely by similar dense infiltrations of young cells. Both lungs showed areas of atelectasis, adjacent alveoli being filled with young myeloid cells. Evidence of further involvement of nonhemopoietic organs was demonstrated by infiltrations of immature cells of granulocytic series into the skin, myocardium, intestine, pancreas, adrenal glands, kidneys, bladder, prostate, epididymis and testes. Skeletal muscle from the dia-

Fig. 4.—Gross appearance of liver at postmortem examination.

phragm was also invaded by these cells. Microscopic study of the skin tumors showed dense infiltrations into the dermis of large pale cells with vesticular nuclei and prominent nucleoli. Many mitotic figures were seen (fig. 3). Sections of bone from rib, femur and sternum showed a basic pattern of dense cellularity which was composed of immature myeloid cells in various stages of development with frequent bizarre mitoses.

The anatomic diagnosis was congenital myelogenous leukemia. The death of the patient was due to subarachnoid and ventricular hemorrhages. Hemorrhage sufficiently extensive into the brain to be the immediate cause of death has been estimated by Leidler and Russell[6] to occur in 29 per cent of patients with leukemia.

## COMMENT

Before a diagnosis of congenital leukemia is made, certain clinical and pathologic requirements should be fulfilled.[1] If the condition is congenital, symptoms should be present at birth or apparent within several days thereafter. Classic findings include enlargement of the liver, spleen and lymph nodes, as well as high

6. Leidler, F., and Russell, W. O.: The Brain in Leukemia, Arch. Path. **40**:14 (July) 1945.

leukocytosis with immature white cells predominating in the blood picture. There should be nothing in the history or laboratory findings suggestive of syphilis or congenital blood dyscrasia, such as erythroblastosis fetalis. Pathologic findings in congenital leukemia characteristically reveal more cellular infiltration into nonhemopoietic sites than could possibly have occurred during the patient's life. Such cellular infiltrations consist of early immature cells and are not due merely to an increase in activity of hemopoietic centers.

The present case seems to satisfy these criteria, despite the fact that several findings resemble those seen in severe cases of erythroblastosis fetalis. While hyperleukocytosis, including numerous early cells of the myeloid and erythrocytic series, occurs in cases of severe erythroblastosis fetalis, the degree exhibited in this particular patient is not typical of erythroblastosis. It is well known that erythroblastosis may be the basis for hepatic and splenic enlargement, hemorrhage and extreme toxicity. Microscopic examination of biopsy specimens and tissues and organs at autopsy in this patient, however, showed such widespread infiltration of young myeloid cells into nonhemopoietic sites that this finding alone argued against the diagnosis of erythroblastosis fetalis. Likewise, the serologic technics currently available revealed no incompatibility between maternal and fetal blood.

Of particular interest in this patient were the widespread tumor-like masses in the skin, which proved on biopsy and postmortem examination to be leukemic myeloid cell infiltrations. As pointed out by Cross,[2d] involvement of the skin in myelogenous leukemia is rare except for purpura, although 1 of the 2 infants with congenital myelogenous leukemia reported on by Cross exhibited leukemic skin infiltrations. These infiltrations, however, were described as excoriations and thick yellow plaques of the skin rather than the tumor-like lesions shown in the present patient and in the one reported on by Morrison and his co-authors.[2a]

In an attempt to explain the occurrence of congenital leukemia, Erf[7] made a survey of infants born of mothers with myelogenous or lymphogenous leukemia during pregnancy and was unable to find a single instance of leukemia in infants born of leukemic mothers. Erf, therefore, concluded that the placenta must be a complete barrier in both directions to leukemic cells. In an experimental study by Erf, guinea pigs which had been inoculated with lipid extracts of placental tissue from a patient with myelogenous leukemia showed cellular changes in body organs characteristic of myeloid cell infiltrations. Control guinea pigs inoculated with normal placental tissue showed no comparable changes.

SUMMARY

The present case report concerns a newborn infant with congenital myelogenous leukemia and multiple leukemic tumor-like infiltrations into the skin. A review of the literature reveals that 16 cases of verified congenital leukemia have been reported. All except 1 were of the myelogenous type. The diagnosis of leukemia in the patient reported on here was verified by hematologic studies of the blood and bone marrow, by skin biopsy and by autopsy observations. No favorable therapeutic response to urethane was noted.

Baylor University College of Medicine (Dr. Taylor).

7. Erf, L. A.: Leukemia and Lymphosarcoma Complicated by Pregnancy: Cellular Changes Produced in Guinea Pigs by Extracts of "Leukemic" Placenta, Am. J. Clin. Path. **17**:268 (April) 1947.

# TRACHEAL COMPRESSION FROM BRONCHOGENIC CYST IN ESOPHAGEAL WALL

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Respiratory difficulty in infancy and childhood requires thorough investigation and prompt treatment. As experience increases, the list of pathologic conditions known to cause chronic respiratory obstruction is being enlarged. One finds that symptoms of tracheal compression in infancy are all too frequently erroneously attributed to enlargement of the thymus. The case here reported illustrates (1) some differential points in the diagnosis of tumor masses compressing the trachea in early life, (2) the importance of early surgical removal of tumors and cysts, especially when there is any narrowing of the airway, and (3) the fact that intramural tumors of the upper part of the esophagus often cause respiratory rather than esophageal symptoms.

## REPORT OF A CASE

D. S., a 2½ year old boy, was admitted to Lenox Hill Hospital on Nov. 26, 1947. The mother had noticed somewhat labored breathing since birth. Palpable rhonchi had been present throughout life. Cyanosis was never observed. A slightly productive cough had been present only in association with colds, which were frequent. There had been no feeding problems and never any difficulty in swallowing. At 2½ years of age the child weighed 35 pounds (15.9 Kg.).

At 3 months of age a roentgenogram of the chest had revealed a mediastinal shadow which was interpreted as an enlarged thymus. At 1 year of age nine roentgen treatments were given without any change in the roentgenologic appearance (fig. 1). During a two year period the patient had been seen by several pediatricians who made a diagnosis of benign mediastinal tumor. None of them advised surgical therapy at that time, although some interference with respiration was obvious. The mother was told that surgical removal might be advisable when the child was several years older. When 2½ years of age, the child was seen for the first time by Dr. Stanley Wershof and Dr. Eli Rubin who considered surgical therapy indicated.

Physical examination revealed a rather well developed and nourished boy. Breathing was slightly labored and noisy. The inspiratory phase was prolonged and associated with slight retraction of the lower end of the sternum and flaring of the costal margins. There was no cyanosis. No cervical masses or lymphadenopathy were present. The chest was slightly emphysematous. Rhonchi were palpable and audible throughout both lungs, but the findings were slightly more pronounced on the right side. Percussion revealed no abnormal dulness. The heart sounds were normal. The results of the remainder of the physical examination were normal. There was no clubbing of the fingers.

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From the Surgical Service, Lenox Hill Hospital.

Roentgenograms of the chest revealed an area of density projecting from the upper part of the mediastinal shadow on the right side (fig. 2*A*). The mass extended considerably above the upper margin of the clavicle on the posteroanterior film. The outline of the area of density was similar to that of an azygos lobe. The trachea was displaced toward the opposite side and was somewhat narrowed.

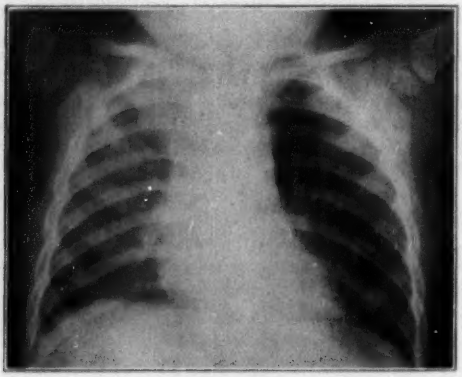

Fig. 1.—Roentgenogram taken at 1 year of age. Note presence of mass in right upper mediastinal region, with diminished aeration of right lung.

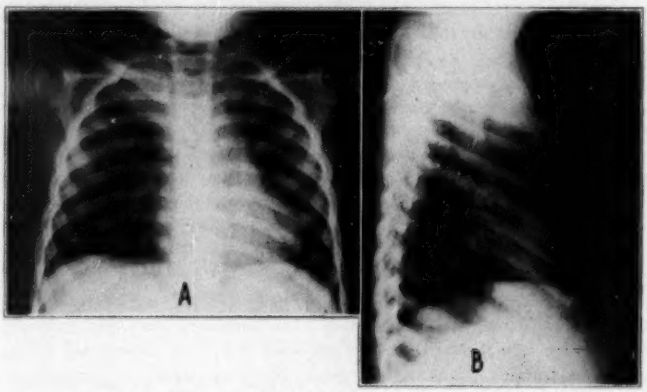


Fig. 2.—Roentgenograms taken at 2½ years of age. *A* shows mass of same contour as on previous roentgenogram. Enlargement of cyst paralleled body growth. Note that the mass extends above clavicular level. *B* is a lateral view showing an ill defined density in the upper prevertebral region.

A lateral view showed an ill defined area of density in the upper part of the posterior mediastinum (fig. 2*B*). No other abnormalities were noted on the roentgenograms. On fluoroscopy no definite change in the contour of the mass was seen with respiration. No esophageal roentgenogram was made.

A positive diagnosis was not made before operation. The presence of an intrathoracic hygroma was considered as a good possibility. Surgical removal was thought to be definitely indicated because of the tracheal compression.

The operation was performed on December 8. With the child under anesthesia induced by intratracheal administration of ether, a right posterolateral transpleural incision was made. A cystic mass was observed bulging from the upper portion of the posterior mediastinum. It lay between the superior vena cava and the vertebral bodies. On dissection a relatively thin-walled cyst bulging from the esophageal wall was encountered. Most of the cyst was not covered by muscle fibers from the esophageal wall, but in a few small areas muscle fibers merged into the wall of the cyst. The medial wall of the cyst lay in apposition to the esophageal submucosa. There was no communication with the lumen of the esophagus. The cyst was removed intact. Following this, there was a 3 cm. defect in the musculature of the esophagus through which the esophageal mucosa bulged. This defect was closed by interrupted sutures. The lumen of the esophagus was not entered during the operative procedure.

Almost immediate improvement in the character of the respirations followed the freeing of the cyst from its confined position in the mediastinum. Cyanosis was not present during the operation.

The postoperative course was uneventful. The pulmonary signs disappeared within a week after operation. The child's appetite improved.

The surgical specimen consisted of a thin-walled cyst measuring 5 by 4 by 4 cm. It contained an opalescent gray fluid. The inner wall was smooth. Microscopic examination showed the inner surface of the cyst to be lined by a pseudostratified columnar epithelium which was partly ciliated. The adjacent loose stroma contained occasional mucous glands and smooth muscle bundles. Striated muscle fibers were present in the outer part of the cyst wall. The diagnosis was bronchogenic cyst.

## COMMENT

Chronic tracheal or bronchial obstruction, even of moderate degree, causes damage to the lungs. Emphysema may result, and secondary pneumonitis often occurs. Even deformities of the thoracic cage, such as grooving of the costal arch, may be produced by the difficulty of inspiration. The absence of cyanosis does not mean that pulmonary ventilation is unimpaired. Moreover, the margin of safety in tracheal compression is often extremely small. A mild infection of the upper respiratory tract may precipitate stridor requiring emergency treatment. Whereas acute laryngeal obstruction can be treated by tracheotomy, no such simple measure is available when the lower part of the trachea is compressed. Thoracotomy must then be undertaken at a far greater risk than when the operation is performed as an elective procedure.

If a posteroanterior roentgenogram of the chest reveals a mediastinal mass which extends above the level of the clavicles and there is no tumor present in the neck, the mass is located in the posterior part of the mediastinum. This one fact alone should have ruled out a normally placed thymus as the explanation of the roentgenologic findings in the case reported. As a matter of fact, a lateral roentgenogram had shown the posterior location of the density.

A mediastinal extension of a cervical hygroma may compress the trachea. If a hygroma or lymphangioma is entirely intrathoracic, it can closely simulate a thymic enlargement.[1] At times, it is difficult to distinguish between benign thymic enlarge-

1. Gross, R. E., and Hurwitt, E. S.: Cervicomediastinal and Mediastinal Cystic Hygromas, Surg., Gynec. & Obst. **87**:599, 1948.

ment and a neoplasm of the thymus. Thoracotomy is indicated in doubtful cases in which tumor is suspected, unless the lesion is obviously beyond surgical help.

Mediastinal lymphadenopathy, inflammatory or neoplastic, can readily be confused with other tumors of the mediastinum. The contour of the shadow, the changes on serial roentgenograms and other findings may aid in differentiation. Compression of the intrathoracic portion of the trachea by a thyroid tumor is extremely rare in childhood.

Intramural tumors of the esophagus are rare, especially in infancy and childhood. Cysts may be observed attached more or less intimately to the esophageal wall; these have been called reduplication cysts or esophageal, gastric or enteric cysts. The lining of such cysts resembles that of some part of the alimentary tract. Most of these cysts cause serious difficulty in early life due to rapid enlargement resulting from the accumulated secretion from the lining glands.[2] In most instances such cysts compress a bronchus rather than the trachea.

Bronchogenic cysts may occur in many places. In addition to an intrapulmonary location, they have been seen in the corynal area, in the hilar region, in the paratracheal, intrapericardial and presternal region, in the wall of the esophagus and even in the vertebral bodies. Bronchogenic cysts usually do not enlarge rapidly and, therefore, often do not cause symptoms until adult life, or they may remain asymptomatic indefinitely. However, a small cyst so located as to cause pressure on adjacent important structures may result in death in early life, usually due to respiratory complications. The subject of bronchogenic cysts of the mediastinum has been summarized elsewhere.[3]

Anomalous blood vessels may cause tracheal and esophageal compression.[4] Roentgenologic studies should include a series with barium sulfate in the esophagus and the outline of the tracheal air column should be visualized. There is usually no widening of the mediastinal shadow, but occasionally an unusual contour may suggest an anomalous course of the aorta or other vascular anomaly.

SUMMARY

All infants manifesting respiratory obstruction should be thoroughly investigated. Too often respiratory difficulty in infancy is erroneously attributed to enlargement of the thymus. Soft cystic tumors can cause serious tracheal compression. A mediastinal tumor which causes any narrowing of the air passages should be removed surgically as soon as recognized, even though it is apparently benign. With proper facilities for anesthetization and thoracic surgical therapy, intrathoracic procedures give good results in early life. The postponement of intrathoracic surgical measures until some arbitrary age is often recommended without logical reason. A bronchogenic cyst in the wall of the esophagus which produced chronic respiratory difficulty is reported. The differential diagnosis of masses in the upper mediastinum in childhood is briefly discussed.

3 East Seventy-First Street.

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3. Maier, H. C.: Bronchiogenic Cysts of the Mediastinum, Ann. Surg. **127**:476, 1948.

4. Gross, R. E., and Ware, P. F.: The Surgical Significance of Aortic Arch Anomalies, Surg., Gynec. & Obst. **83**:435, 1946.

# CONGENITAL TRICUSPID ATRESIA IN A BOY TWELVE YEARS OF AGE

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The congenital cardiac malformation, tricuspid atresia, is usually attended by distinctive clinical features. The clinical diagnosis is based on the presence of cyanosis, roentgenographic findings suggestive of absence of the right ventricle and the presence of left axis deviation in the electrocardiogram. The malformation usually causes death early in infancy; in the majority of cases, the patients die when less than 1 year of age. It is the purpose of this report to relate the clinical and pathologic findings in a case of congenital tricuspid atresia in which the patient lived more than twelve years and in which the correct diagnosis had been made clinically.

## REPORT OF A CASE

In January 1948, the patient, who was a white boy, was first observed by two of us (H. M. R. and J. A. C.) when he was 11½ years old. His chief complaints were dyspnea and fatigue. At the time of his birth, on Aug. 22, 1936, cyanosis had been observed. It had persisted and had become more intense when the infant cried.

During the early period of the patient's life, he had gained weight slowly and his muscular development had been retarded. He had not been able to walk until his second year, and his physical stamina had always been poor. The mental development had been normal. These symptoms had forced him to lead a sedentary life. Fatigue and dyspnea had occurred after he walked two city blocks. At the time of his examination, he was unable to attend school, but prior to this he had advanced to the fourth grade.

Physical examination revealed an underdeveloped white boy with intense cyanosis of the skin and mucous membranes. His height was 52 inches (132 cm.) and his weight was 54 pounds (24.5 Kg.). The pulse rate was 70 beats per minute. The systolic blood pressure in each arm was 110 mm. of mercury and the diastolic pressure was 70 mm. The apical impulse of the heart was situated in the left fifth intercostal space at a point 8 cm. from the midsternal line. There were no thrills or murmurs. The second cardiac sound was of greater intensity than the first sound. This difference was most prominent in the left third intercostal space. Examination of the lungs did not disclose any abnormality.

The spleen was palpable 6 cm. below the left costal margin, and the lower edge of the liver extended 3 cm. below the right costal margin. There were

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no pulsations at the margin of the liver. Examination of the extremities revealed decided clubbing of the fingers and toes. There was intense cyanosis of the nail beds.

Roentgenoscopic examination of the thorax revealed cardiac enlargement. In the anteroposterior view the enlargement was predominantly to the left. There was a concavity in the expected site of the shadow of the pulmonary conus. In the left anterior oblique view, the left ventricle appeared enlarged and the right ventricle rudimentary. The pulmonary window was abnormally clear. No increase in the width of the shadow of the great vessels was observed in the left anterior oblique view. The roentgenoscopic findings were confirmed by roentgenographic examination (fig. 1 *a* and *b*).

The electrocardiogram revealed a pronounced degree of axis deviation to the left (fig. 2), normal sinus rhythm, prominent P waves in lead II and inversion of the T wave in lead IV (CF).

Examination of the blood revealed 8,020,000 erythrocytes per cubic millimeter and 26.4 Gm. of hemoglobin per hundred cubic centimeters of whole blood. The

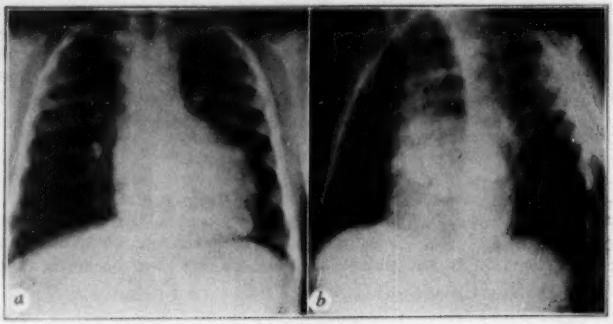


Fig. 1.—Anteroposterior roentgenogram (*a*) of thorax showing cardiac enlargement. A concavity exists at the expected site of the shadow of the pulmonary conus. Left anterior oblique roentgenogram (*b*) of thorax. The straight outline of the left margin of the heart may be interpreted as indicative of lack of development of the right ventricle. The enlarged clear pulmonary window is indicative of absence of a normal-sized pulmonary trunk.

leukocytes numbered 5,000 per cubic millimeter of blood. A differential blood count revealed the following percentage distribution of the leukocytes: polymorphonuclear neutrophils, 48 per cent; lymphocytes, 42 per cent; eosinophils, 6 per cent; basophils, 1 per cent, and monocytes, 3 per cent. Examination of the urine did not reveal any abnormality.

The clinical diagnosis was congenital tricuspid atresia. During the period of observation there were no changes in the patient's condition. In August 1948, he was referred to the Mayo Clinic for surgical treatment. At the clinic, the clinical and laboratory findings were similar to those already recorded. The oxygen saturation of a sample of blood taken from a radial artery while the patient was resting was 54 per cent. It was believed that the patient would receive benefit from a Blalock-Taussig operation. On August 24, in the early part of the operation, after the thorax had been opened but before any dissection of the great vessels had been started, the patient suddenly died.

Necropsy did not disclose any specific reason for the sudden death. The points of chief interest were in the heart and great vessels. Examination disclosed tricuspid atresia, transposition of the great vessels and subpulmonary stenosis. Externally, the ventricular part of the heart appeared enlarged, and the apex was rounded. The aorta arose anteriorly and hid the pulmonary trunk from view when the front of the specimen was examined. The right auricular appendage was in an abnormal site. It lay to the left of the great vessels and superior to and to the right of the left auricular appendage (fig. 3).

Examination of the interior of the right atrium revealed that the venae cavae and the coronary sinus entered this chamber normally. At the expected site of the tricuspid valve there was a small depression in the atrial floor, but examination

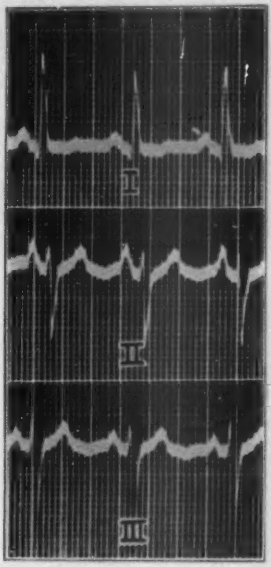


Fig. 2.—Electrocardiogram made Jan. 28, 1948, showing decided axis deviation to the left and prominent P waves in lead II.

failed to disclose a tricuspid orifice or any tissue identifiable as that of the tricuspid valve (fig. 4 *a*). The only outlet of the right atrium was a defective atrial septum through which right atrial blood could flow into the left atrium.

The atrial septum was represented by a relatively thin gray membrane which was attached superiorly, posteriorly and inferiorly. The anterior free margin of the atrial septum was crescent shaped, thereby producing an atrial septal defect which lay between the free anterior margin of the atrial septum behind and the anterior atrial wall between the ostiums of the right and left atrial appendages in front. The defect measured 1.5 cm. from before backward and 2 cm. from above downward. The defect had the position and shape of the interatrial foramen secundum in septum primum, which is normally closed by the interatrial septum

Fig. 3.—Left anterior view of the opened heart. The lower part of the large ventricular chamber has been removed. The aorta is wide and lies anterior and parallel to the pulmonary trunk (*P.T.*). The pulmonary trunk is more narrow than is normal. As in the second case of Huebschmann (*Verhandl. d. deutsch. path. Gesellsch.* **18**:174-192, 1921), the two auricular appendages lie to the left of the great vessels. *R.A.* indicates the right auricular appendage and *L.A.* the left auricular appendage.

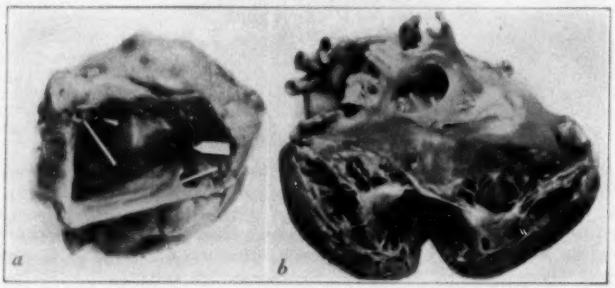


Fig. 4.—(*a*) the interior of the right atrium. At the tip of the pointer, the expected site of the tricuspid orifice, there is neither an opening nor a tissue recognizable as that of an atrioventricular valve. The lower probe lies in the ostium of the coronary sinus. One of the two upper probes is in the superior vena cava; the other lies in the patent foramen ovale. (*b*) the left side of the heart. There is a patent foramen ovale which represents the main outlet for blood which enters the right atrium. There also are several fenestrations of the atrial septum inferior to the foramen ovale. These represent additional, yet minor, points of communication between the two atriums. The mitral valve is properly formed. Its orifice leads from the left atrium into a large left-sided ventricular chamber.

secundum (fig. 4*b*). Extending posteriorly and inferiorly on the right side of the atrial septum from the upper aspect of the defect was a slightly raised prominence. This probably represented the upper limbus of the fossa ovalis, but there was no vestige of a lower limbus. An interatrial septum secundum had evidently been incompletely formed. In the lower portion of the atrial septum, there was a fenestrated zone represented by several small defects measuring up to 4 by 3 mm. in diameter (fig. 4*b*).

The left atrium received the pulmonary veins and also communicated with the right atrium through the septal defects described. The left atrium communicated with the ventricular part of the heart through a normally formed and wide mitral valve, measuring 11.5 cm. in circumference.

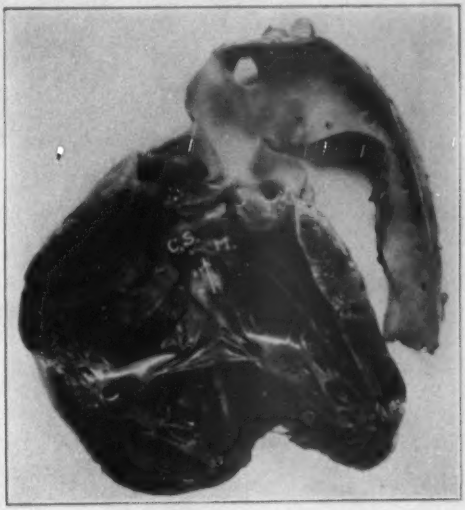


Fig. 5.—The ventricular part of the heart opened and viewed anteriorly. The wide aorta is in free communication with the ventricular part of the heart, arising both from the large left-sided ventricular chamber and the smaller right-sided chamber. The arrow points to the ventricular ostium of the unopened stenotic subpulmonary tract. The coronary arteries arise from the aorta. *C.S.* is the crista supraventricularis and *M.* the anterior leaflet of the mitral valve.

The ventricular part of the heart showed an interesting structure (fig. 5). Most of it was composed of a large left-sided chamber. There was a much smaller chamber which lay along the right upper aspect of the main ventricular mass. The ventricular part was divided into a large and a small chamber by two muscular bundles. One of these bundles extended vertically upward from the right wall of the larger chamber. The other mass was represented by a ridge of muscle which extended obliquely downward and to the right from the posterior wall of the ventricular outlet. The lower margin of this bundle, all of which was considered the crista supraventricularis, lay in the posterior wall of the smaller ventricular chamber slightly to the right of the vertical mass of muscle described. Anterior

to the crista supraventricularis and above the vertical mass of muscle was a space through which the larger and smaller ventricular chambers communicated freely.

The upper limit of the crista supraventricularis was closely approximated to the ventricular surface of the anterior leaflet of the mitral valve. A bridge of fibrous tissue extended between the neighboring aspects of the anterior leaflet of the mitral valve and the crista supraventricularis. This tissue completed the structure of a narrow subpulmonary tract which was bounded by this bridge anteriorly, by the posterior wall of the ventricle behind, by the crista supraventricularis to the right and by the anterior leaflet of the mitral valve to the left (fig. 6). At the inlet, the subpulmonary tract measured only 3 mm. in diameter. Immediately above the inlet, the tract widened to measure about 1 cm. in circum-

Fig. 6.—The opened stenotic subpulmonary tract and the interior of the larger left-sided ventricular chamber. The tract has the following boundaries: the posterior wall of the large ventricle, behind; the anterior leaflet of the mitral valve (*M.*), to the left; the crista supraventricularis (*C.S.*), to the right, and a bridge of fibrous tissue which extends between the latter two structures, in front. One leaflet (*P.V.*) of the bicuspid pulmonary valve is shown. The arrow points to the opened ventricular ostium of the subpulmonary tract.

ference. The tract measured 1 cm. in length, and at its upper end it communicated with the pulmonary orifice.

Above this narrow tract were the pulmonary orifice and trunk. The pulmonary orifice and trunk were more narrow than the corresponding portions of the aorta but wider than the subpulmonary tract. The pulmonary orifice measured 1.5 cm. in diameter. The pulmonary valve was bicuspid but not stenotic. The pulmonary trunk terminated by dividing into right and left pulmonary arteries.

In contrast to the pulmonary trunk, the aorta communicated freely with the ventricular part of the heart. The aorta arose anterior and somewhat to the right

of the pulmonary orifice above the communication between the two ventricular chambers. It measured 5.5 cm. in circumference. There were three normally formed aortic leaflets. The coronary arteries arose from the aorta. The ascending aorta lay anterior to and somewhat to the right of, and parallel to, the pulmonary trunk. The branches of the aortic arch were normal. The ductus arteriosus was closed. The course of the aortic arch and of the descending aorta was normal. From the descending aorta arose several prominent bronchial arteries which were identified as somewhat tortuous vessels running from the aorta to each lung along the posterior aspect of the respective major bronchi (fig. 7).

Fig. 7.—The heart and lungs. Extending from the descending thoracic aorta to the posterior aspects of the major bronchi are prominent bronchial arteries.

COMMENT

In this case, the history of cyanosis from birth was a feature of paramount importance in deciding that the basis for the cardiac disease was congenital. In a case of cyanotic congenital cardiac disease in which the patient lives for more than twelve years, the anatomic type of malformation is usually the tetralogy of Fallot. In this case, however, there were aspects which were inconsistent with the diagnosis of the tetralogy of Fallot but which, at the same time, were consistent with the diagnosis of tricuspid atresia. These aspects were electrocardiographic and roentgenologic. The electrocardiogram showed left axis deviation. This is contrary to the finding in cases of the tetralogy of Fallot, as well as in other forms of cyanotic

congenital cardiac disease, except tricuspid atresia. With rare exceptions, left axis deviation in a case of cyanotic congenital cardiac disease is virtually diagnostic of tricuspid atresia.[1]

Roentgenologically, tricuspid atresia and the tetralogy of Fallot have certain features in common, while certain differences exist between the two conditions. In the anteroposterior view, concavity in the region of the shadow of the pulmonary conus is common to both conditions. This feature was present in our case. Another feature which the two conditions have in common is an abnormally clear pulmonary window in the left anterior oblique view. This finding was also present in our case. The roentgenologic view just named may, however, yield findings of importance in differentiating the two conditions. In the tetralogy of Fallot there is evidence of enlargement of the right ventricle, while in tricuspid atresia there is a picture of an underdeveloped right ventricle.[2] The latter was present in our case. This, along with the left axis deviation in the electrocardiogram, was considered important evidence in favor of tricuspid atresia and, at the same time, against the tetralogy of Fallot. On the basis of these findings, the diagnosis of a specific type of congenital cardiac malformation, namely, tricuspid atresia, was made clinically. The absence of cardiac murmurs in our case was supportive though not diagnostic evidence of tricuspid atresia instead of the tetralogy of Fallot. In another communication, one of us (J. E. E.) and Burchell [1d] presented a classification of reported cases of congenital tricuspid atresia based on the anatomic characteristics of the heart. Basically, that classification was an elaboration of the one presented in 1906 by Kühne [3] and later supported by other authors.[4] Into one group were placed those cases of tricuspid atresia in which there was no transposition of the great vessels. In the other group were placed those cases in which the tricuspid atresia was associated with transposition. Each major group was then subdivided. The first group was subdivided into cases in which tricuspid atresia was associated with pulmonary atresia and closed ventricular septum on one hand and subpulmonary stenosis on the other. The second group was subdivided into cases in which the tricuspid atresia was associated with pulmonary or subpulmonary stenosis, of which the case here reported is an example. The second subgroup of the second group included those cases in which neither pulmonary nor subpulmonary stenosis was present. In a review of the histories of the cases studied, it was of interest that in cases of tricuspid atresia in which the patients lived beyond childhood the anomaly universally belonged to the group into which the anomaly in our case falls, that is, tricuspid atresia with transposition of the great vessels and with pulmonary or subpulmonary stenosis (type IIa of the

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2. Taussig.[1a] Brown.[1b] Taussig.[1c]

3. Kühne, M.: Ueber zwei Fälle kongenitaler Atresie des Ostium venosum dextrum, Jahrb. f. Kinderh. **63**:235-249, 1906.

4. Brown.[1b] Wieland, E.: Zur Klinik und Morphologie der angeborenen Tricuspidalatresie, Jahrb. f. Kinderh. **79**:320-343, 1914.

classification cited). The case of Hedinger,[5] in which the patient was a 56 year old woman, and which often has been cited as an example of unusually long survival in tricuspid atresia, belonged to this group. It will be recalled that in our case the bronchial arteries were observed to be unusually dilated. It is conceivable that the unusual longevity in Hedinger's [5] case might have been explained by the compensatory mechanism of a relatively great volume of blood carried to the lungs through similar channels.

SUMMARY

This report is based on a case of tricuspid atresia in which the patient, who was a boy, lived for more than twelve years. The clinical diagnosis was made on the basis of persistent cyanosis which had been present since birth, left axis deviation in the electrocardiogram and roentgenographic evidence of an enlarged left ventricle and a rudimentary right ventricle. Pathologically, the tricuspid atresia was associated with transposition of the great vessels and with a severe degree of subpulmonary stenosis. It is believed that the unusual length of survival in this case might have resulted from the compensatory function of the enlarged bronchial arteries.

The Mayo Clinic.

5. Hedinger, E.: Transposition der grossen Gefässe bei rudimentärer linker Herzkammer bei einer 56 jährigen Frau, Centralbl. f. allg. Path. u. path. Anat. **26**:529-535 (Nov.) 1915.

# HEMANGIOENDOTHELIOMA OF THE LIVER IN INFANCY

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Hemangioendothelioma of the liver in infancy is a rare condition. Kunstadter[1] in 1933 reviewed 14 cases from the literature and added 1 case of his own. Since then, additional cases have been reported by Howard,[2] Schwartz,[3] Andries and Kaump,[4] Dodrick,[5] Schumann,[6] Blauel[7] and Berezin, Sharnoff and Stein.[8] Because of the rarity of the disease, we wish to record an additional case.

## REPORT OF A CASE

The patient was a 2 month old white male infant who was born at full term after a medically induced labor. The mother was Rh negative and the baby Rh positive, but there had been no rise in Rh titer during pregnancy. Shortly after birth, three pinhead-sized reddish macular spots were noted on the infant's body. They gradually increased in size to that of a small pea. Meanwhile, a number of similar lesions was noted appearing on other portions of the skin. At the age of 4 weeks, the baby was treated for diarrhea and tenesmus. At that time, moderate pallor, slight hepatic enlargement and a soft systolic apical murmur were noted. With treatment the diarrhea improved in several days. There had been no fever, jaundice or cyanosis.

*Physical Examination.*—On his admission to the pediatric service a slight pallor was noted. Twenty-one macular and papular hemangiomas varying from pinhead to pea size were scattered over the face, chest, abdomen, buttocks and extremities. A systolic thrill was palpable in the left parasternal region, and

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From the Division of Pathology, Department of Laboratories, Sinai Hospital.

1. Kunstadter, R. H.: Hemangio-Endothelioma of the Liver in Infancy, Am. J. Dis. Child. **46**:803 (Oct.) 1933.
2. Howard, W. A.: Multiple Hemangio-Endotheliomas of the Liver, J. Pediat. **8**:588 (May) 1936.
3. Schwartz, A. R.: Multiple Malignant Hemangio-Endothelioma in an Infant, Arch. Pediat. **62**:1 (Jan.) 1945.
4. Andries, G. H., and Kaump, D. H.: Multiple Malignant Hemangiomas of the Liver, Am. J. Clin. Path. **14**:489 (Sept.) 1944.
5. Dodrick, J. R.: Multiple Malignant Hemangio-Endotheliomas in an Infant, Am. J. Dis. Child. **55**:559 (March) 1938.
6. Schumann, H. D.: Beitrag zur Kasuistik des primären Hämangioendothelioms der Leber, Frankfurt. Ztschr. f. Path. **55**:1, 1941.
7. Blauel, I.: Ueber das Hämangioendotheliom der Leber bei Kindern, Monatsschr. f. Kinderh. **91**:345, 1942.
8. Berezin, S. W.; Sharnoff, J. G., and Stein, J. D.: Primary Hemangioendothelioma of the Liver in Infancy, New England J. Med. **238**:906 (June 24) 1948.

a harsh systolic murmur was heard over the entire precordium. The abdomen was slightly distended. The edge of the liver was palpable 3½ fingerbreadths below the costal margin.

*Laboratory Data.*—The red blood cell count was 3,250,000. The hemoglobin concentration was 9.8 Gm. (66 per cent). The white blood cell count was 9,150, with 50 per cent polymorphonuclear leukocytes, 2 per cent eosinophils and 48 per cent lymphocytes. The serologic test for syphilis gave a negative reaction. The blood cholesterol was 185 mg. per hundred cubic centimeters. The thymol

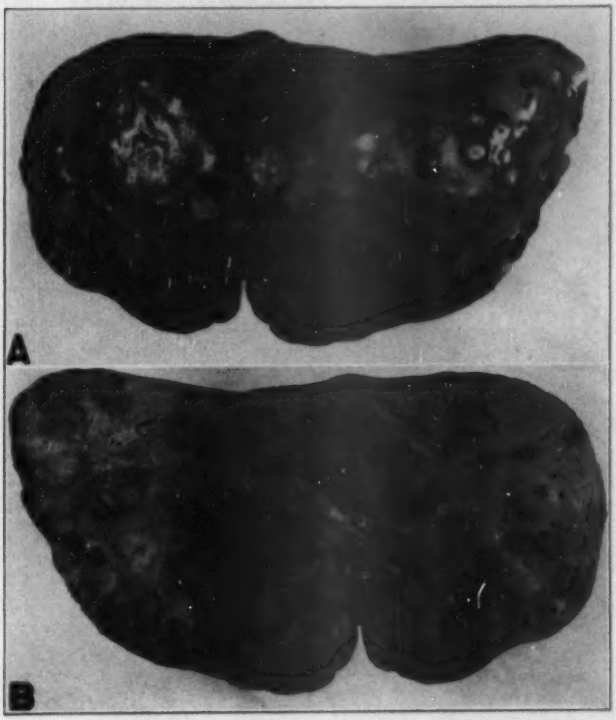


Fig. 1.—Photographs of liver showing tumor nodules (*A*) on surface and (*B*) on cut surface.

turbidity was 3.9 units. The test with sulfobromophthalein sodium U. S. P. showed 30 per cent retention in thirty minutes. The blood albumin was 5.3 Gm. and the globulin 2.7 Gm. per hundred cubic centimeters. The indirect van den Bergh reaction was 0.1 mg. and the direct van den Bergh reaction was 0.0 mg. per hundred cubic centimeters. Roentgenologic examination of the chest showed slight cardiac enlargement, that of the abdomen revealed the edge of the liver to extend down below the crest of the ilium and that of the long bones showed nothing abnormal.

Fig. 2.—Photomicrographs of tumor nodule in liver; *A* is a low power view and *B* a high power view.

*Course in the Hospital.*—Six days after his admission, two new hemangiomas were noted on the patient's skin. On the tenth day in the hospital an exploratory laparotomy was performed, and biopsy specimens of the liver and of the skin lesions were taken. One hour after operation the patient suddenly became cyanotic and died.

*Autopsy Observations.*—Gross Examination: Scattered over the skin surfaces there were approximately twenty-five well defined reddish, sessile, nodular tumors. They were moderately firm and varied in size from less than 0.1 to 0.3 cm. in diameter. Most of these projected slightly above the surface of the skin. They were present on the face, neck, chest, back, buttocks and extremities. The liver was considerably enlarged and weighed 425 Gm. On the surfaces of the liver and within the hepatic parenchyma there were many well circumscribed tumor nodules which varied in size from 0.2 to 1.2 cm. (fig. 1). These nodular areas had a varied appearance. Most of them were fairly firm and grayish. Others were grayish red, yellowish red or white. Some of the larger ones were surrounded by hemorrhagic zones and showed central umbilication. On the mucosal aspect of the cecum there was a 0.2 cm. projecting grayish brown nodule which was covered by an intact but somewhat granular mucosa. The lungs showed moderate edema and congestion. The other organs showed no gross abnormalities.

Microscopic Examination: The skin lesions, the nodules in the liver and the single nodule in the cecum showed a similar histologic appearance and, therefore, are described together (fig. 2). The tumor tissue consisted essentially of numerous vascular channels. In the skin, there was a resemblance in some places to adult blood vessels of a capillary type. In most areas the linings of the vascular channels were composed of groups and rows of atypical endothelial cells. These were large and showed hyperchromatic nuclei. Others had vesicular nuclei with distinct nucleoli. The cells were elongated or ovoid. A distinct reticulum was demonstrated around the vascular channels. In some areas there were demonstrated only anastomosing cords and rows of cells which formed an interlacing network but did not show formation of any lumens. In no place was there any evidence of encapsulation. The tumor tissue in the liver contained remnants of portal fields as manifested by the presence of scattered bile ducts.

## COMMENT

Vascular tumors may be divided into the benign and malignant varieties. The benign forms may be single or multiple and may vary considerably in size. A benign metastasizing form has been described, but, according to Jaffé[9] and Stout,[10] its existence is doubtful. Malignant vascular tumors are relatively rare. Theoretically, they are derived from the three essential components of blood vessels—the endothelial cells, the perithelial cells and the smooth muscle fibers. Of these, the hemangioendothelioma is the commonest. The hemangiopericytoma has been reported by Stout and Murray.[11] As far as is known, no case of leiomyosarcoma of vascular origin exists in the literature.

9. Jaffé, R. H.: Multiple Hemangiomas of the Skin and of the Internal Organs, Arch. Path. **7**:44 (Jan.) 1929.

10. Stout, A. P.: A Tumor of Blood Vessels Featuring Vascular Endothelial Cells, Ann. Surg. **118**:445 (Sept.) 1943.

11. Stout, A. P., and Murray, M. R.: Hemangiopericytoma, Ann. Surg. **116**:26 (July) 1942.

The term hemangioendothelioma was first used by Mallory [12] in 1908. However, a wide variety of names have been applied to malignant vascular tumors—endothelioma, endotheliоblastoma, endotheliosarcoma, hemangioendotheliоblastoma, angioblastoma and angioma hypertrophicum.

In the cases reviewed, the patients ranged in age from 36 hours to 4½ years. The neoplasm was commoner in females. In reports in which the sex of the patient was given, 15 cases occurred in females and 8 in males. No familial tendency is apparent. In 3 cases there were associated congenital anomalies.

The clinical picture in infants is fairly characteristic. Gradual abdominal enlargement is usually observed in the first month or two of life. Gastrointestinal disturbances, such as constipation, diarrhea, vomiting and abnormal stools, are common. Anemia is usually present. Jaundice and ascites are rare, having occurred in only 4 of the cases. The disease process is progressive in its course, death usually occurring within six months.

Single or multiple hemangiomas of the skin are fairly common and were present in our case, as well as in 7 of the 25 cases reviewed. Other sites involved were the retroperitoneal lymph nodes, vertebrae, ribs, lungs, adrenal glands, kidneys and, in our case, the cecum.

At autopsy the liver is enlarged and its surfaces are covered by nodular tumor masses of a moderately firm, soft or cystic consistency and varying from dark reddish purple to yellowish white. On section, the nodules may be seen to contain liquid or clotted blood, but frequently the tumor masses are solid and contain hemorrhagic foci.

Microscopically, Stout [10] gave two criteria which are uniformly present and must be fulfilled before a diagnosis of hemangioendothelioma can be made. The first is the formation of atypical endothelial cells in greater numbers than are required to line vessels with a simple endothelial membrane. The second is the formation of vascular tubes with a delicate framework of reticulin fibers and a pronounced tendency for their lumens to anastomose.

The individual cells may vary considerably from elongated to rounded forms. The cytoplasm is eosinophilic and finely vacuolated. The nuclei are vesicular. Mitotic figures are rarely seen. The endothelial cells may proliferate to form solid sheets of cells with scant stroma or to form only a single continuous layer. There is no encapsulation. A silver reticulin stain is helpful in bringing out the supporting framework and accentuating the pattern. If the cells are grouped inside the vessel, the cells are endothelial, while if the cells lie outside the vessel wall one is dealing with pericytes.

According to Foote,[13] the disease in infancy is congenital and arises from an embryonic endothelium. In adults, the tumor may be due to fetal inclusions which have remained dormant for a long time or arise from a benign angioma in which the endothelium has reverted to an embryonic form. Howard [2] was of the opinion that a hemangioendothelioma present since birth should be considered as a congenital defect or anomaly of the vascular system. In regard to multiple vascular tumors, he stated:

"It is logical to suppose that the hemangiomas will not necessarily be confined to any one location. Rather than consider these tumors as malignant with invasive

12. Mallory, F. B.: The Results of the Application of Special Histological Methods to the Study of Tumors, J. Exper. Med. **10**:575, 1908.

13. Foote, J.: Hemangioendothelioma of the Liver, J. A. M. A. **73**:1042 (Oct. 4) 1919.

qualities, we might well classify them as multiple tissue defects. . . . The variability of their location makes the theory of metastases seem unlikely and unnecessary."

Taylor and Moore[14] pointed out that, although with an increased growth energy factor metastases may occur, we may be dealing with primary multiple tumors with functional stimuli of an unknown nature acting on blood vessels. According to Rabson,[15] the widespread occurrence of malignant vascular tumors in the body can be attributed to true metastases, as well as to a multiple primary origin. In our case, the presence of isolated tumor nodules in the skin and cecum and of multiple nodules in the liver favors the theory of coincidental multiple tumors of congenital origin.

SUMMARY

A case of hemangioendothelioma of the liver with similar tumor involvement of the skin and cecum occurring in an infant is presented.

The sites of involvement in our case are more likely explained on the theory of coincidental multiple tumors of congenital origin, rather than by the theory of metastasis.

The characteristic clinical and pathologic findings are presented.

Sinai Hospital (5).

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14. Taylor, A. C., and Moore, E.: Multiple Hemangiomas Showing Certain Malignant Characteristics in an Infant, Am. J. Cancer **19**:31 (Sept.) 1933.

15. Rabson, S. M.: Multiple Mesenchymal Hemendothelioma, Arch. Path. **25**:185 (Feb.) 1938.

# Progress in Pediatrics

## TREATMENT OF THE PATIENT WITH CLEFT PALATE

### Present Day Concepts of a Pediatric Responsibility

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THE CONGENITAL malformation of cleft palate and cleft lip presents one of the most challenging problems in pediatrics. Appearing as it does in 1 of every 700 live births, there is no pediatrician who has not dealt with any number of these children and their harassed families. Unfortunately, too often pediatrics does not fulfil its obligations but passes the problem on to surgery where the best in technical and mechanical help may be obtained. Surgical repair is performed, and the child relegated to the mercies of society and spotty medical and dental care. It is because of this responsibility that it was felt that a consideration of the guidance of the over-all care of these patients would be of interest.

It is the pediatrician who initiates discussion and counsel concerning the infant's future with the grief-stricken parents. The baby's nutrition must be maintained, and it must be kept free of infection and respiratory distress during the early months of life. A competent surgeon must be obtained in consultation and his suggestions considered. Preoperative and postoperative care must be carefully supervised. Operative closure of the lip, and perhaps later of the palate, must be decided on. Subsequently dental care, speech training and improvement in facies must be gained. The psychologic problems of the growing child beset with deformed appearance and unintelligible speech must be managed. From the best of such care will come the adolescent and the adult—a medical failure, lost to society, or a vigorous adapted person, salvaged to lead as full a life as his inherent abilities permit.

Obviously, no one physician can cope with all the aspects of this problem. Therefore, the pediatrician profits immeasurably by the cooperative help of members of other professions whose work makes them peculiarly competent in various facets of the situation. One such concerted effort has been made by the Lancaster Cleft Palate Clinic—a nonprofit organization of specialists in each phase of the care of these patients. The group includes physicians, surgeons, dentists, orthodontists, speech therapists, a psychologist and various laboratory technicians. Each member of the clinic sees every patient, evaluating his

From the Lancaster Cleft Palate Clinic.

particular field per se and in relation to the whole person. The group then participates in a round table discussion and correlation of opinions and plans the future program of care needed. The concepts outlined in this paper are the outgrowth of the experience of this group in dealing with more than 1,500 persons with oral clefts during the past twelve years.

## ETIOLOGIC FACTORS

Embryologically, these malformations are created in the oral cavity during the first six to eight weeks of gestation. They may be due either to inadequate approximation of the various components of the palate and lip or to defective bridging of proliferative epithelial structures between adjacent anatomic parts. In large series, 30 to 50 per cent of the patients have evidence of a hereditary factor.[1] Evidence suggests both dominant and recessive pedigrees with probable sex-linked and autosomal genetic structures further complicating matters.[2] Interestingly, there is a male preponderance, with left-sided involvement occurring with greater frequency than right. The amount of disability appears to depend on the degree of penetrance and the type of genetic determinant.

Extensive research with laboratory animals under controlled conditions of inbreeding,[3] injection of pituitary preparations,[4] exposure to roentgen rays and deficiency diets [5] has shown that phenocopies of the hereditary forms may be produced. These studies provide material for speculation concerning the importance of these and other environmental factors in producing individual anomalies of this type and in facilitating their appearance in patients with a pedigree of susceptible genetic makeup.

## CLASSIFICATION

Cases of cleft palate and cleft lip are classified according to the severity of the anatomic defect seen in the patient. The lip may be affected per se in 20 to 25 per cent of patients and the palate alone in 25 to 30 per cent. The remaining 45 to 50 per cent of patients have

1. Sanders, J.: Inheritance of Harelip and Cleft Palate, Genetica **16**:433-510, 1934. Fogh-Anderson, P.: Inheritance of Harelip and Cleft Palate: Contribution to the Elucidation of the Etiology of the Congenital Clefts of the Face, translated by E. Aageson, Copenhagen, Arnold Busck, 1942.

2. Csik, L., and Mather, K.: The Sex Incidence of Certain Hereditary Traits in Man, Ann. Eugenics **8**:126-145 (Jan.) 1938. Fortuyn, A. B. D.: Inheritance of Harelip and Cleft Palate in Man, Genetica **17**:349-366, 1935.

3. Steiniger, F.: Neue Beobachtungen an der erblichen Hasenscharte der Maus, Ztschr. f. menschl. Vererb. -u. Konstitutionslehre **23**:427-462, 1939.

4. Steiniger, F.: Ueber die experimentelle Beeinflussung der Ausbildung erblicher Hasenscharten bei der Maus, Ztschr. f. menschl. Vererb. -u. Konstitutionslehre **24**:1-12, 1939.

5. Warkany, J.: Etiology of Congenital Malformations, in Levine, S. J., and others: Advances in Pediatrics, New York, Interscience Publishers, Inc., 1947, vol. 2, pp. 1-63.

defects of both palate and lip. Considering the malformation of the palate to be the deciding element, my associates and I utilize Veau and Borel's criteria for classifying them (fig. 1)[6]:

I. Cleft of soft palate
II. Cleft of soft and hard palates
III. Cleft of soft and hard palates with unilateral premaxillary cleft
IV. Cleft of soft and hard palates with bilateral premaxillary cleft

Not only is this scheme for grouping such deformities of academic significance but it is invaluable for determining the needs of these patients for surgical, medical, dental and speech therapy.

## CLEFT LIP

The most pressing problem in patients with oral defects is that of the lip. Its cleft requires skilful surgical correction for good cosmetic result, for strengthening of the anterior portion of the maxilla and for guidance of subsequent growth in this area. However, there is no need

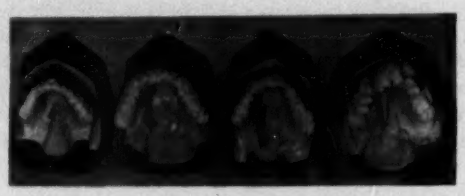

Fig. 1.—Classification of palatal clefts, types I to IV.

to rush the patient to the operating room for closure. The friable tissues of the newborn are made stronger by the passage of time. The infant's nutritional status reaches a balance with progressive gain in weight in the early months of life. The risk of anesthetization and operation in the older infant is greatly lessened by this improved physical condition. We, therefore, advocate repair of the lip at about 3 or 4 months of age, when the pediatrician feels that the infant is gaining well and is free from infection.

The difficulty experienced in feeding during this early part of life can be met by one great force—patience. Various devices, such as eye-dropper, Brecht feeder or a medicine glass from which the baby may drink, have been used successfully. As the infant becomes more skilful in manipulating its tongue against the sides of the palate, the nipple may be introduced with good result. In rare patients, gavage is the only means of feeding that will permit survival. In any event, we have

6. Veau, V., and Borel, S.: Division palatine, anatomie, chirurgie, phonétique, Paris, Masson & Cie, 1931.

had little need for obturator closure of the cleft or for nipples designed with an additional flange to close the defect while the infant is sucking.

The plastic repair of the lip is usually completed in a single stage procedure. At times, secondary problems arise from thickening of the healing scar, from the loss of contour of the lip or from drooping of the tip of the nose. These require secondary stages of repair, with good cosmetic results usually being obtained. In general, the plastic surgeon accomplishes a miracle of improvement in facial appearance, parental uplift and revitalization of the morale of the family group which enables them to face the future.

### MEDICAL AND DENTAL CARE

Growth and development continue in these patients with the usual dental and medical problems arising; however, their defect imposes additional difficulties with respect to respiratory infections and dentition.

The exposed mucous membrane of the nasal cavity is readily subject to mechanical trauma and infection. This may result in copious secretions, with the creation of a persistent site of infection that may endanger the lower tracheobronchial tree and parenchyma of the lung. Close observation and adequate therapy of such complications are necessary to prevent their becoming a hazard. Furthermore, the possibility of palatal surgical intervention closing off such drainage and forming pockets of infected mucus and sinusitis must be considered.

Anomalies of the alveolar ridge of the maxilla will cause gross deformities as teeth appear along its margins. These will require expert dental and orthodontic treatment to preserve all the elements that can be saved. Diligent cleaning and fluoride treatments have served to prolong their life and usefulness. Prompt filling or extraction of decayed members further promotes good oral hygiene.

### CLEFT PALATE

In contrast to the cleft lip, which lends itself readily to surgical treatment with good result, the cleft palate poses many conflicting aspects which must be evaluated in each patient. There are some groups who advocate early plastic repair of the palatal defect by any one of a number of ingenious procedures.[7] Their major premise holds that without such repair at an early age (4 to 18 months) little hope can be offered for future appearance, speech or psychologic stability. Our observations have been contrary to this premise; hence we deal with the problem from an entirely different approach.

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7. Vaughan, H. S.: The Surgical Correction of Congenital Cleft Palate, S. Clin. North America **24**:370-380 (April) 1944. Dorrance, G. M., and Bransfield, J. W.: Studies in the Anatomy and Repair of Cleft Palate, Surg., Gynec. & Obst. **84**:878-885 (April 15) 1947. Oldfield, M. C.: Modern Trends in Harelip and Cleft Palate Surgery, Brit. J. Surg. **37**:178-194 (Oct.) 1949.

When it is recalled that at birth the relationship of face to skull is as 1 is to 9, and that by adolescence this has altered to a ratio of 1 to 2, the significance of growth and development in these patients looms in its proper magnitude. The maxillary portion of the face grows tremendously in all directions—anteroposteriorly, laterally and vertically. This development moves at great speed early in life to gain about five-sixths of its maximum by the time the child is 5 years of age.[8] The remaining one sixth, especially downward and forward growth, continues to 20 years of age. Furthermore, it has been demonstrated that the tissues comprising the palatal defect maintain their respective relationships, losing nothing that might be of value in late repair.[9]

At this time of decision, there are many patients for whom surgical therapy does not offer the best result and may even be contraindicated. In these patients the continued efforts of dentist and orthodontist are

Fig. 2.—*A*, type III cleft with little tissue available for adequate surgical closure. Orthodontic treatment was utilized. *B*, adequate closure with complete functional result with plastic appliance filling the alveolar defect, closing the cleft and aiding speech.

required to reach satisfactory results. Their procedure is carefully to prepare models of the patient's mouth and to create an obturator for closure of the existing defect (fig. 2). In addition, a speech bulb is designed to replace the missing tissue of the soft palate. This appliance permits closure of the air stream of speech as needed for good enunciation. It serves as the second element in the valvelike separation of the nasopharynx from the oropharynx by the bulging forward of the muscles of the posterior pharyngeal wall in Passavant's cushion.

8. Slaughter, W. B., and Brodie, A. G.: Recent Research in Facial Clefts, Plast. & Reconstruct. Surg. **4**:311-332 (July) 1949. Graber, T. M.: Craniofacial Morphology in Cleft Palate and Cleft Lip Deformities, Surg., Gynec. & Obst. **88**:359-369 (March) 1949.

9. Peyton, W. T., and Ritchie, H. P.: Dimensions and Growth of the Palate in Infants with Maldevelopment of the Upper Lip and Palate, Arch. Surg. **33**:1046-1053 (Dec.) 1936.

Contrary to some misconceptions of patients being "doomed" to wearing an obturator, this form of therapy has proved to be a godsend to many patients with cleft palate both with and without surgical repair. Present day technics and materials permit the construction of obturators which fit the palate perfectly, aid speech and improve the general appear-

Fig. 3.—Suction type of plastic obturator and speech bulb for child.

Fig. 4.—Laminagram of child's speech bulb in place in the pharynx.

ance of the patient. They may be worn with ease from the age of 4 or 5 years. The type for small children is quite simple and is held in place by suction (fig. 3). Obturators may be altered with growth of the child but actually do not require many changes. Later, the permanent obturators that attach to the teeth by clasps may be prepared and will require little alteration after the child is 14 years of age (fig. 4). This procedure

then provides an excellent means of closing the defect with assured improvement in facies, in speech and in the psychologic adjustment of the child.

In some patients who have had successful surgical treatment, use of a form of appliance may also be necessary. Many persons with clefts have had excellent closure of the hard palate but have persistent absence of the soft palate. Secondary surgical procedures, such as push-back operations and skin grafts, may permit some reconstruction of this portion; however, these represent major procedures and may produce results of questionable value.[10] In such circumstances, the use of a simple speech bulb, projected backward from clasps to the teeth, provides a good substitute for the irreplaceable soft palate tissue. Individualized fitting and adaptation to the bulb promote rapid improvement in speech under the guidance of a competent speech therapist.

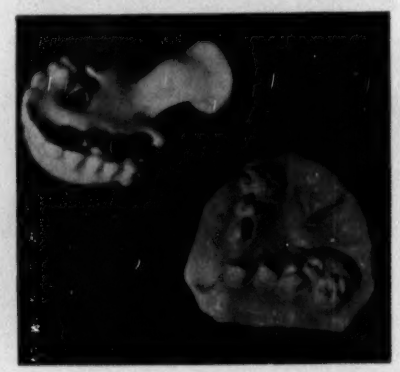

Fig. 5.—Model of maxillary deformity due to damaging effect of early surgical intervention. The orthodontic appliance was designed to improve cosmetic appearance, close cleft and facilitate speech.

In the Lancaster Clinic, we have seen several patients to whom surgical intervention has actually done a disservice. Their palates are grotesquely deformed, and further intervention would be unthinkable. Some have persistent cicatrized orifices in the hard palate, while others show conspicuous effects of damage to growth centers, with complete collapse of the maxillary structures. In many of these, it is possible

10. Dorrance, G. M., and Bransfield, J. W.: The Push-back Operation for Repair of Cleft Palate, Plast. & Reconstruct. Surg. **1**:145-169 (Sept.) 1946. Baxter, H.: Use of Skin Grafts in Repair of Cleft Palate to Improve Speech, Arch. Surg. **59**:870-881 (Oct.) 1949. Kazanjian, V. H.: Secondary Deformities in Cleft Palate Patients, Ann. Surg. **109**:349-367 (March) 1939.

to get some semblance of improvement with prostheses designed to correct the disability (fig. 5).

On comparison of the results from surgical and obturator therapy—and we have seen both at work—there is much to be said on both sides. Furthermore, both sides should be well considered before any forward step is taken in the treatment of the child with a cleft.

### SPEECH TRAINING

Along with cosmetic appearance, speech disability represents one of the main problems in patients with cleft palate. The very nature of the defect prevents adequate control of the air stream within the pharynx and creates the characteristic unintelligible nasal speech. Even with closure of the hard palate, the soft palate deficit persists. In this situation, some surgical procedures are of value, but use of the speech bulb

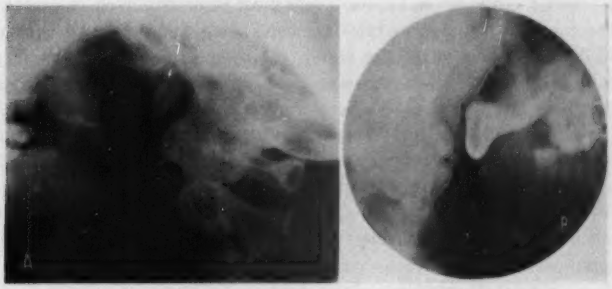

Fig. 6.—*A*, laminagram demonstrating the width of the uncontrolled air stream of speech in patient with foreshortened palate. Passavant's cushion is outlined by radiopaque material. *B*, laminagram demonstrating position of speech bulb and narrowing of airway to facilitate valve action of Passavant's cushion in reducing nasality and improving speech.

has given our patients almost uniformly good results. The position of the bulb is well demonstrated in figure 6, which shows the width of the air stream of speech and the control possible with the bulb in place. However, use of the appliance is only a portion of the total effort for speech. Speech training of the most arduous and persistent kind is a prime necessity.

Children who are followed in the clinic receive simple lessons from 3 to 4 years of age in an effort to build up control and strength of the muscles concerned. Audiometric examinations are made to insure adequate hearing and understanding of the spoken voice. As they receive surgical or orthodontic treatment, speech training is expanded in its scope to utilize fully the advantages of closure of the palate. In children

in whom the need exists, the speech bulb is fitted and further progress facilitated. With this new control of the air stream, nasality is decidely diminished and words become much more intelligible.

With success apparent in this embarrassing phase of the life of the patient with cleft palate, his whole concept of relationship to his fellows is improved. The afflicted child may now both face and speak to others without fear of ridicule or derision—the desired triumph of all concerned.

### PSYCHOLOGIC ASPECTS

From the first revelation of the cleft palate deformity in the newborn, psychologic problems are manifold. The thoughts, the fears and the misgivings of the family represent a sudden overwhelming mental crisis. The parents then are the ones that must be dealt with first, consideration of the child's needs coming later. Ignorance of the true nature and the cause of the deformity must first be expelled. A careful explanation of the hopes for the future must be given. Help in accepting the infant and courage to face the world with their shared misfortune are needed. Too often, the family recalls a person with cleft palate whom they have known and who may have led a life marred by disfigurement and despair. It, therefore, is of paramount importance that they receive guidance and encouragement, not only from the psychologist but from all others who touch their lives. We have found that giving the parents an opportunity to visit the clinic, to meet members of the staff and to see similar children moving toward successful attainment does wonders in accomplishing this purpose. With further understanding comes hope and from that the help that will be needed to aid in solving the future problems of the child.

The child's problems do not arise until he comes of an age to realize that some difference from others exists in his appearance and speech. If by this time the family, the neighbors and the playmates are accustomed to the child's shortcomings, his adjustment to his environment may move along quite smoothly. However, if cruel rejection and misunderstanding have been thrust on the patient, the scars are long in healing and may be apparent throughout his lifetime.

The increase in understanding and ability of the older child permits greater strides in correction of defects and disabilities. The plan for surgical repair or orthodontic treatment gets under way with concrete results, offering hope for future improvement. Continued speech therapy provides additional stimulation for progress. The eager, adjusted child responds readily to such forces and will move uneventfully into adolescence, proving a match both mentally and physically for his classmates. Such children are assured of their rightful place in the world of adults that they will soon enter.

Unfortunately, many patients have not had the benefit of the complete care that we have found necessary for them. In every case, besides physical deformities, the patient had deep-rooted mental and psychologic disabilities. The pitiful quandary of these patients requires the utmost of combined group effort and psychologic guidance to salvage that which remains.

In any circumstance, entrants at the clinic receive complete psychometric testing as one of the first studies. This evaluation of their mental status is extremely important for determining their true intellectual capacities for treatment and adjustment. In addition, the child's relationships and attitudes with respect to society are such an integral part of his final rehabilitation that early recognition of these characteristics is an absolute necessity. Many patients with cleft palate who have been shunned or ill treated by others tend to withdraw from social contact, become reticent to express themselves or display outright belligerence. Because of these changes, they are incorrectly labeled as behavior problems or as mentally retarded and they continue to be rejected by society. It is, therefore, necessary to have a complete understanding of the child's capacities and maladjustments so that the group may best handle the peculiarities of each patient. Continued efforts to correct these disturbed mental patterns, fully to utilize mental abilities and to improve progressively the patient's appearance and speech are the keys to success in treatment of these children.

## PUBLIC HEALTH CONSIDERATIONS

Statistical studies indicate that oral clefts are one of the most frequent of congenital anomalies. Furthermore, patients with these deformities have a high incidence of survival and propagate with continuation of the genetic pattern that will produce more cases in the future. In addition, despite extensive research, the appearance of phenotypes continues with unabated frequency. These factors presently show no evidence of declining; hence the case load of patients with cleft palate will undoubtedly persist and will probably rise with an increased birth rate.

This situation, along with the high degree of potential rehabilitation possible in these persons, calls for an increase in numbers and improvement in quality of clinics to deal with them. At present, the Lancaster Cleft Palate Clinic has served as a pilot study in the field and has been visited by interested groups from many parts of the United States and abroad. Such interest on the part of professional persons will, no doubt, stimulate the creation of similar clinics throughout the country, bringing a program of "complete care of the whole person."

The cost of care of these patients continues to be a large stumbling block in their treatment. We have found the clinic method to be the best and least expensive way to handle the situation. Furthermore, as state and federal funds are expended for rehabilitation and research in these cases, the problem of cost will be more easily managed.

## CONCLUSIONS

The patient with cleft lip and cleft palate has too often not received the necessary complete evaluation and treatment that correction of his disability requires. Because this is a congenital defect and needs repair by the time the child reaches adolescence, it is the responsibility of the pediatrician to undertake the over-all guidance of the child. He must aid in correlating all the factors that enter into the complete treatment of the whole person. Our experience has shown this to require the closest cooperation among physicians, surgeons, dentists, orthodontists, speech therapists and psychologists. We, therefore, advocate that, wherever possible, these patients be given the benefit of such care.

The infant with cleft lip should be permitted to gain adequate nutritional stability before closure is attempted. This is usually not before the third or fourth month, when good plastic surgical repair is indicated.

The closure of the palate should be evaluated by both a competent plastic surgeon and an orthodontist, with broadminded consideration for each other. Their intent should be primarily to provide the patient with the best long term result possible. Whatever the decision, the optimal time for intervention is 4 to 6 years of age.

The improvement of speech is one of the main goals in therapy and requires expert and diligent efforts. Training should be supplemented by surgical treatment or use of speech appliances when indicated.

Throughout all the foregoing, it is imperative that the family and the patient have a firm grasp of the emotional and psychologic elements of their problem. An understanding and sympathetic environment should be maintained by neighbors, by playmates and by teachers in an effort to promote the fullest in individual expression and mental growth.

The undertaking of such a constructive program of care for these children has led to a most satisfactory salvaging and rehabilitation of whole persons rather than mere closure of holes in their mouths. We advocate the creation of more such clinics with governmental financial aid administered on a community level.

## SUMMARY

Patients with problems of cleft palate and cleft lip are best managed by clinic groups, correlating the efforts of physicians, surgeons, dentists, orthodontists, speech therapists and psychologists.

The cleft lip presents a plastic surgical problem that lends itself best for closure when the infant is 3 to 4 months of age. The closure of the cleft palate is best approached when the child is 4 to 6 years of age, the choice of plastic surgeon or orthodontist depending on the particular case. Good speech training and use of speech bulb appliances have been found to give uniformly the best results in this phase. Psychologic adjustment of family and patient is most essential in the over-all rehabilitation program. The problem of oral defects shows no trend of decrease and presents a need for long range programs of diagnosis and treatment. This appears to be best handled by a clinic group and warrants the financial support of government agencies.

26 North Lime Street.

# Abstracts from Current Literature

## Metabolism; Infant Feeding; Milk and Other Foods

Amino Acids in the Blood and Urine of Human Subjects Ingesting Different Amounts of the Same Proteins. Betty F. Steele, May S. Reynolds and C. A. Baumann, J. Nutrition **40**:145 (Jan. 10) 1950.

Four college students were placed on diets supplying 25, 100 and 200 Gm. of protein daily contributed by meat, milk and bread, and the urinary excretion and blood levels of amino acids were determined microbiologically. The authors present the following data: The excretion of histidine, serine, alanine and tyrosine increased rather markedly with an increase in dietary protein but not proportionally to the intake. Increasing the intake of protein had little effect on the excretion of most other amino acids or on the "fasting" levels of the individual amino acids in the plasma. The nonessential amino acids—histidine, glutamic acid, cystine, aspartic acid, alanine and serine—occurred most abundantly in acid-hydrolyzed urine. The essential amino acids were excreted in much smaller amounts. Much individual variation in the excretion of amino acids was evident.

Fredeen, Kansas City, Mo.

Glycogen Disease Resembling Mongolism, Cretinism and Amytonia Congenita. David H. Clement and Gabriel C. Godman, J. Pediat. **36**:11 (Jan.) 1950.

The authors report a case of the cardiomuscular type of glycogen disease. This patient, who died at the age of 6 months, presented the clinical picture of cretinism with macroglosia, generalized muscular hypotonia and cardiac enlargement, but the thyroid function was apparently normal. Mongolism was suggested, but there was no evidence of mental retardation. On this basis and because of the generalized muscular weakness, amytonia congenita was suspected. Autopsy proved the diagnosis of glycogen disease. In this case, deposition of glycogen in the central nervous system was a prominent feature.

Macdonald, Pittsburgh.

Comparison of Nutritive Value of Mineral-Enriched Meat and Milk. Irvine McQuarrie and M. R. Ziegler, Pediatrics **5**:210 (Feb.) 1950.

The nutritive value of cooked lean meat enriched with calcium, phosphorus and other minerals, as well as with fat, carbohydrate and vitamins, was compared with that of whole cow's milk in feeding experiments on young growing rats and on 2 adolescent boys. As judged by changes in body weight, analyses of the whole carcass, bone composition, analyses of blood serum, character of the furry coat and spontaneous motor activity, growing rats thrived at least as well on the meat as on the milk regimen, when the two diets contained the same amounts of calcium phosphorus, magnesium and potassium, as well as protein, fat, carbohydrate and vitamins.

The meat formula without any mineral enrichment or with either calcium or phosphorus omitted from the salt mixture failed to support normal growth and normal bone composition in the rat.

Preliminary nitrogen, phosphorus and calcium balance studies on 2 adolescent human subjects showed the meat enriched with calcium and phosphorus to be as good as or slightly better than milk as a source for these elements.

FROM THE AUTHORS' SUMMARY.

STUDIES OF NUTRITION IN NEWFOUNDLAND CHILDREN. KATHLEEN SCOBIE, BERTHA S. BURKE and HAROLD C. STUART, Canad. M. A. J. **60**:233 (March) 1949.

The diet of children in a Newfoundland orphanage is compared with that of children from a small town and its environs. This orphanage diet was found to be adequate in all respects, with perhaps less vitamin C available than would be considered optimal. The diet of the families in the town was lacking in milk and vitamins C, A and D. The physical condition of the children in the town was far inferior to that of the wards of the orphanage.

McGUIGAN, Evanston, Ill.

SWEETENED CONDENSED MILK IN INFANT FEEDING. G. SKODACEK, Pediat. listy **3**:203, 1948.

The author reports his experiences obtained at the clinic of Prof. Glanzmann in Berne, Switzerland, in the use of sweetened condensed milk in feeding both normal and ill infants.

FROM THE AUTHOR'S SUMMARY.

CHRONIC NUTRITIONAL DISTURBANCE IN THE NURSLING. ANIBAL ARIZTIA and TEODORO ZENTENO, Rev. chilena de pediat. **19**:171 (Feb.) 1948.

Results are presented of an analysis of 973 case histories of dystrophic infants treated at the Hospital de Niños Luis Calvo Mackenna, Santiago, Chile, from 1943 to 1947. This series was composed only of children up to 2 years of age, hospitalized for at least one week, whose serious nutritional damage derived from exogenous causes, faulty nutrition, infection or defective hygiene. All forms due to specific causes, such as syphilis and tuberculosis, congenital abnormalities, constitutional disturbances and the avitaminoses with their characteristic anatomicopathologic lesions, were excluded.

The study was planned to search especially for: (1) etiologic factors that determine dystrophy, (2) analysis of different signs and symptoms, physical as well as functional, of the condition and (3) effects of medical treatment on duration of convalescence, time of hospitalization and mortality. The following chief facts may be drawn from this study:

1. Dystrophy is a common condition in young infants, especially prevalent during the first months of life. Among the variety of factors that may lead to it, dietary deficiency appears to be of greatest importance, followed by infections and acute nutritional disturbances. Endogenous factors play a secondary role.

2. The more serious damage of dystrophy is observed, as a rule, during the first quarters of life and in older infants in whom the condition has been prolonged for several months. They are demonstrated by pronounced metabolic disturbances (hypoproteinemia, low nutritional tolerance, dysergia) due, probably, to serious parenchymal damage, especially in the liver.

3. The duration of convalescence depends more on the severity of dystrophy than on the type of treatment, a long hospitalization being necessary, averaging ten weeks, to assure recovery and prevent relapses.

In prophylaxis of dystrophy the following measures are recommended: (1) preventive medical aid to infants at hospital outpatient and well baby clinics, work

that should be completed at home by public health nurses; (2) free baby foods to families of low income that are unable to provide an adequate diet for their infants; (3) prompt medical care and hospitalization, whenever it is necessary, of infants whose condition is complicated by infections or acute nutritional disturbances, as well as of those who do not show a definite improvement with ambulatory treatment in a brief time, and (4) while the general condition of living for the lower classes remains unsatisfactory, establishment of convalescent homes which will considerably reduce the present high cost of care for dystrophic infants.

FROM THE AUTHORS' SUMMARY.

## Vitamins; Avitaminoses

FURTHER STUDIES ON THE RELATIONSHIP BETWEEN ILLUMINATION AND THE ASCORBIC ACID CONTENT OF TOMATO FRUITS. G. F. SOMERS, K. G. HAMNER and W. C. KELLY, J. Nutrition **40**:133 (Jan. 10) 1950.

Experiments with plants in sand culture indicate that the intensity of illumination is effective in influencing the ascorbic acid content of tomato fruit only to the extent that the fruits themselves are directly illuminated. Apparently the intensity of illumination of the vines alone has a smaller effect, if any. Moreover, about three weeks is required to obtain the full effects of a change in illumination. No doubt there existed considerable differences in the degree of foliation and the resultant relative shading of the individual fruits by the leaves.

FREDEEN, Kansas City, Mo.

THERAPEUTIC RESEARCHES WITH CITRIC ACID IN RICKETS. W. WINKLER, Ann. paediat. **172**: 129 (March) 1949.

The therapeutic value of citric acid was examined in 10 patients with rickets and five patients with tetany due to rickets. One group received 5 Gm. (75 grains) of sodium citrate three times daily, another one 0.5 Gm. (7½ grains) of citric acid in whole milk five times daily. A third group was treated with citric acid and half milk in which the calcium-citric acid quotient was stabilized at 4.3. A fourth group was given citric acid in quarter milk which had the same quotient and was brought up to equal caloric value with the addition of fat, amino acids and sugar. Slight increases in phosphorus were observed and moderate ones in the third group; in the patients with tetany there were rises in the calcium values, but they were neither therapeutically sufficient nor permanent. Roentgenologically there were no signs of healing. Phosphatase rose during the treatment. This form of treatment may be of theoretic interest, but the drug is therapeutically not efficient enough.

FROM THE AUTHOR'S SUMMARY.

AMOUNT AND IMPORTANCE OF BLOOD CITRIC ACID IN RICKETS. TRUDI OCHSE, Ann. paediat. **172**: 139 (March) 1949.

Using the method evolved by Pucher, Ochse estimated the citric acid in the blood of healthy children, in rachitic children and in rachitic children who had been treated with vitamin D. In the healthy and the rachitic children the results vary around the same averages, but the values in the rachitic children before the vitamin D stoss therapy are (average) about 97 mg. per hundred cubic centimeters higher than after the vitamin D stoss, i. e., the citric acid level in the blood of the rachitic children decreases after the vitamin D stoss. This decrease of

citric acid after vitamin D therapy is statistically significant. A patient with rickets which proved to be refractory to vitamin D had the highest value for citric acid before the vitamin D stoss. The value decreased temporarily after very large doses of vitamin D.

FROM THE AUTHOR'S SUMMARY.

NEW VIEWPOINTS IN HIGH DOSAGE VITAMIN D THERAPY. HANS JESSERER, Wien. klin. Wchnschr. **62**:129 (Feb. 24) 1950.

Pure vitamin D exercises antirachitic activity in microgram doses, whereas milligram doses are required to increase resorption of calcium from the intestinal canal and to increase renal excretion of phosphate. Dihydrotachysterol, as well as pure synthetic vitamin $D_3$ and the natural $D_3$, all three in large doses, increases blood calcium; but tachysterol, dihydrotachysterol and toxisterol have no antirachitic potency. All three are effective in diseases which are not due to vitamin deficiency, such as parathyroid or enterogenic hypocalcinemia, when given in adequate doses by mouth. Dihydrotachysterol and vitamin $D_2$ given intramuscularly are ineffective, while vitamin $D_3$ given intramuscularly is effective but the effect is somewhat delayed. Vitamin $D_3$ given intravenously is as effective as when given by mouth. In cases in which the blood calcium became normal after oral administration of any of the three substances a normal level usually could be maintained by intramuscular administration of vitamin $D_3$. It is of importance that in cases of tetany on a rachitic basis—a real vitamin D deficiency disease—intramuscular administration of vitamin $D_3$ is not effective immediately. Vitamin $D_3$ under these conditions acts more slowly than on oral administration but considerably more rapidly than vitamin $D_2$. It is recommended that 15 mg. of vitamin $D_2$ be given intramuscularly for prophylaxis of rickets. The danger signs of vitamin D therapy in high dosage and dihydrotachysterol are discussed.

AMBERG, Rochester, Minn.

## Hygiene; Growth and Nutrition; Public Health

ANALYSIS OF PREMATURE MORTALITY RATES. E. B. PLATTNER, ALBERT F. STEIN and HAROLD X. GERBER, Pediatrics **5**:193 (Feb.) 1950.

From 1941 to 1946, 2,910 premature infants were admitted to the premature station of the Children's Division of Cook County Hospital. Of this number, 17.9 per cent died. The influence of birth weight on survival rate was demonstrated. There were more female premature infants than male (1.23:1). The female infants had a higher survival rate than the male infants (15.3 per cent for females as compared with 21.9 per cent for males).

There were more nonwhite than white premature infants in this series. The nonwhite infants had a mortality rate of 15.7 per cent, whereas the white infants had a mortality rate of 20.6 per cent. Possible explanations for this difference included the racial factor and the factor of transportation of a prematurely born infant from one place to another.

Of the infants born at Cook County Hospital, where the factor of transfer was nonexistent, nonwhite infants had a mortality rate of 16.3 per cent; the white infants, 21.1 per cent. Female infants survived better than did the male infants (female mortality rate, 13.4 per cent male mortality rate, 22.2 per cent).

Of the infants transferred to Cook County Hospital, the white infants survived better than the nonwhite (21 per cent as compared with 25.3 per cent). The female infants in this group likewise showed greater survival ability than did the male infants (20.2 per cent for females; 24.1 per cent for males).

There was no month of the year in which prematurity was consistently higher than in the other months. The death of prematurely born infants likewise is not influenced by the month of the year. The mortality rate is related to the number of admissions and not to month or season.

FROM THE AUTHORS' SUMMARY.

CURRENT PROBLEMS IN DEATHS OF PERSONS UNDER 20 YEARS OF AGE AS EVIDENCED BY A STUDY OF THE SITUATION IN THE PAST DECADE IN NEW YORK CITY. LEONA BAUMGARTNER and VIVIAN PESSIN, Pediatrics **5**:257 (Feb.) 1950.

A comparative study was made of the decline in mortality rates for children in New York city from 1937 to 1946. Death certificates filed by physicians there contain certain confidential medical data, and it is these data which have been used as the basis for this study. Mortality rates for the following age groups are analyzed: under 1 year, 1 to 4, 5 to 9, 10 to 14 and 15 to 19 years. Figures on fetal deaths are included. The leading causes of death in each age group are indicated as well as changes in their relative importance through the years. The authors came to the following conclusions.

In the past ten years mortality rates for persons under 20 have declined less rapidly than in previous decades. Nevertheless, application of new and well recognized procedures in the prevention of deaths due to pneumonia, influenza, appendicitis, diarrhea, contagious diseases and tuberculosis have led to striking reductions in deaths due to these causes. Because of these reductions, other causes of death have assumed new importance. Thus, for children over 1 year of age accidents are today the leading cause of death. Heart disease, tuberculosis and cancer claim a high percentage among persons from 10 to 20 years, while contagious diseases and diseases of the respiratory tract are still important for children under 10 years.

For infants, the deaths occurring before, at or near birth are of chief importance, with those associated with premature birth assuming an importance that demands active and immediate attention. Despite the gains made, deaths associated with childbirth (i. e., fetal and neonatal deaths) stand second today in claiming lives of all ages in New York city citizens. Only heart disease has a larger mortality. The time has come for physicians to take cognizance of these facts and to see that all mothers and babies get the kind of care which good pediatricians and obstetricians know can be given. In addition, there is a pressing need for an intensified research program to the end that deaths in infancy and those due to accidents and heart disease may more effectively be prevented.

## Prematurity and Congenital Deformities

METHYL TESTOSTERONE AND PLASMA FOR PREMATURE INFANTS. A. M. EARLE, J. Pediat. **36**:87 (Jan.) 1950.

Each of 11 premature infants was given 5 mg. of methyltestosterone and 100 to 150 cc. of plasma orally daily. Their average daily gain in weight was more than double that of a control group. The average length of hospitalization was twenty-five days for the treated group and fifty-eight days for the controls.

MACDONALD, Pittsburgh.

ADVANTAGES OF A SEPARATE NURSERY FOR PREMATURE INFANTS. STUART LANE AREY and MARY P. CHRISTIANSEN, Minnesota Med. **32**: 384 (April) 1949.

In this paper the authors discuss the care of the premature infant in a private hospital. From January 1940 through October 1947, a total of 272 such infants were taken care of. Up to 1945 this was accomplished in the regular nursery of the maternity ward. After that a separate premature nursery was established. This consisted of two rooms with an adjoining utility room, one room for clean and one for isolation cases. This setup was entirely separate from the newborn nursery, being on another floor. It was manned by a separate staff. A graduate nurse was on duty 24 hours daily. Emphasis was placed on the fact that a comparison of results before and after the establishment of a separate premature nursery revealed a lowering of premature mortality by approximately one half. Care by interested graduate nurses in a separate nursery is a most important factor in lowering the death rate among premature infants.

STOESSER, Minneapolis.

EXPERIMENTAL USE OF METHYL TESTOSTERONE IN PREMATURE INFANTS: PRELIMINARY REPORT. JOSEPH N. SEITCHIK and HORST A. AGERTY, Pediatrics **5**:200 (Feb.) 1950.

Fifty-seven premature infants weighing between 1,300 and 2,300 Kg. were studied in respect to time required to regain birth weight, time to attain an arbitrarily chosen weight and rate of weight gain. Twenty-seven infants received methyltestosterone. These infants demonstrated no evidence of stimulation of growth.

In view of the meager metabolic effects of methyltestosterone in premature infants, there appears to be little justification for its use for such infants.

FROM THE AUTHORS' SUMMARY.

FETAL TOLERANCE TO ROENTGEN RAYS. ARTHUR A. HOBBS, Radiology **54**:242 (Feb.) 1950.

A pregnant woman, 29 years of age, with an adenocarcinoma of the breast had a postoperative osteolytic lesion in the sacrum and right ilium. The latter was discovered when the fetus was 4½ months old. Roentgen radiation (1,500 r) was delivered to each of two 15 cm. portals for a calculated midpelvic depth dose of 900 r. The osseous lesion increased during treatment. An additional dose (375 r) was administered when the fetus was taken at 7½ months and the pregnancy was terminated. Soon thereafter the bone lesion healed. Death followed the development of osteolytic lesions in others bones. The child was normal at the age of 16 months and apparently was experiencing no ill effects of the prenatal roentgen therapy received.

ANSPACH, Chicago.

EFFECT OF PLASMA THERAPY ON THE GROWTH OF THE PREMATURE INFANT. L. LANDUCCI, Lattante **20**: 89 (Feb.) 1949.

If the premature infant is to gain in weight as fast as it would have done in utero, it must have, to meet its protein needs, as much as 290 cc. of breast milk per kilogram of body weight daily. Various means have been tried to meet this high protein requirement of premature infants, whose digestive system does not tolerate feeding well. Landucci has made use of dried American plasma. The dried plasma was diluted to normal strength, and 50 cc. was given intravenously to each of 11 premature infants. In 8 cases the transfusions acted as an immediate

stimulus for an increase of weight; in the other three cases, a second transfusion was necessary before the weight gain became apparent. In six of the cases, the transfusion was followed by a definite increase in the amount of milk which the child could tolerate by mouth. Four underweight babies responded well by starting to gain in weight after one to three transfusions of the human plasma.

HIGGINS, Boston.

PROBLEM OF ACHONDROPLASIA (CHONDRODYSTROPHY). J. REICHARD, Paediat. danub. **5**: 214 (March-April) 1949.

The etiology of achondroplasia may be explained by the assumption that some factor causes a decrease of the blood supply to the fetus at the period of cartilage development. Besides the so-called achondroplastic dwarfism, the rare and grave form of achondroplasia, less grave, partial, atypical achondroplasia must also be diagnosed. Micromelia, i. e., shortness of limbs, is an essential symptom. Cases lacking that feature, such as cases of late chondrodystrophy, etc., do not belong among the real chondrodystrophies. A case of achondroplastic twins is reported. The fact that one of the twins showed amnionic deformities supports Reichard's assumption that amnionic pressure may also have a pathogenetic role.

FROM THE AUTHOR'S SUMMARY.

## Newborn

THE NITROGEN PARTITION IN NEWBORN INFANTS' URINE. A. BARLOW and R. O. MCCANCE, Arch. Dis. Childhood **23**:225 (Dec.) 1948.

The total nitrogen in urine formed in utero averaged less than 100 mg. per hundred cubic centimeters. When physiologic dehydration was greatest, the total nitrogen averaged 812 mg., but this was not so high as the average figure obtained for normal adult urine. During the first week of life the outputs of total and urea nitrogen, expressed as milligrams per kilogram of body weight per day, tended to rise but were always much lower than in normal or starving adults. They were about equal to the outputs of adults on high calory–low protein diets. The output of uric acid nitrogen in milligrams per kilogram of body weight per day was also much lower than in normal or starving adults, but there was no tendency for it to rise. When the partition of nitrogen in infants' urine was compared with that in normal adults' urine, it was observed that the percentage present as urea was lower, that the percentage present as ammonia, uric acid and undetermined nitrogen was higher and that the percentage present as creatinine was about the same. The percentage of total nitrogen present as urea was significantly higher in the urine formed in utero and after the third day of life than in that passed in the first two days of life.

KELLY, Milwaukee.

THE DEVELOPMENT OF THE AEROBIC BACTERIAL FLORA OF THE THROAT IN NEWBORN BABIES. JAY WARD SMITH and ARTHUR L. BLOOMFIELD, J. Pediat. **36**:51 (Jan.) 1950.

As a result of studies on 6 newborn infants, the authors believe that nonhemolytic streptococci are the basic aerobic bacterial flora of the throat. They appear twenty-four hours after birth and probably persist throughout life. Staphylococci appear irregularly and are not a part of the indigenous flora. The administration of penicillin delays the appearance of the streptococci but does not alter the basic flora.

MACDONALD, Pittsburgh.

"Green Stool Syndrome" of the Newly Born Infant. I. J. Greenblatt, Harry Bloch, R. D. Turin and S. David Sternberg, Pediatrics **5**:180 (Feb.) 1950.

In newborn infants, a syndrome consisting of green stools and normal number of bowel movements without pyrexia, dehydration, vomiting or death is described. No etiologic agent was determined, but metabolic changes, evidenced by low prothrombin levels and absence of urobilin in the feces and urine, were seen.

The appearance of a normal bacteriologic flora of the feces as evidenced by culture, smear and the presence of urobilinogen and normal prothrombin activity following treatment suggests that a penicillin-sensitive agent which exerted antibiotic effects on the normal intestinal flora was present.

From the Authors' Summary.

Fetoinfantile Septic Infection. A. Minujin, M. Rapaport and C. Muniagurria, Rev. Soc. puericult. Buenos Aires **14**:117 (July-Dec.) 1948.

The authors present the clinical histories of 3 newborn infants who died of congenital septic infection: vascular pneumonia, encephalitis and appendicitis, respectively. These 3 children were delivered at full term, of mothers clinically healthy, after a normal pregnancy and easy delivery.

They consider a form of sepsis in newborn infants which is not recognized as such, owing to the few clinical manifestations and the lack of systematic necropsies.

They draw attention to the fact that the fetoinfantile sepsis acquired by contagion with the mother in fetal life could be transmitted through the placenta without signs of illness in the mother or signs of alterations in the placenta. This could occur because the placenta is not a filter for the germs and because a septic focus which is tolerated by the mother may give subclinical bacteremia.

The Society of Puericulture of Buenos Aires was requested to undertake the study of this form of infection and to recommend necessary measures of prophylaxis and treatment in order to protect the fetus and the newborn infant from septic infections during prenatal life, that is, before, during and after parturition.

From the Authors' Summary.

Morbus Hemolyticus Neonatorum on the Basis of Incompatibility Within the ABO-Systems. J. Schwarz and P. Speiser, Wien. klin. Wchnschr. **62**:63 (Jan. 27) 1950.

From a summary of observations on 10 cases of hemolytic disease of the newborn, it is evident that, besides the diseases of the newborn conditioned by rhesus factors, like or similar diseases may be referable to incompatibilty of the classic blood groups in mother and child.

Amberg, Rochester, Minn.

The Cause of Death in Newborn Infants with Breech Presentation and the Therapeutic Consequences. Hans Heidler, Wien. klin. Wchnschr. **62**:78 (Feb. 3) 1950.

On the basis of investigations of the author reported about twenty years ago and further data from the literature, it is reemphasized that the main cause of death of newborn infants on breech delivery is intracranial hemorrhage in about 80 per cent and that asphyxia is culpable in about 20 per cent. The injuries are produced in the majority of the cases by the manual assistance. To reduce the resistance of

the soft parts, episiotomy is advisable, particularly in primiparas. The freeing of the infant's arms and the delivery of the head must be accomplished without undue force, aided by intravenous injection of pituitary.

AMBERG, Rochester, Minn.

## Acute Contagious Diseases

POLIOMYELITIS IN FAMILIES ATTACKED BY THE DISEASE. HERBERT A. WENNER and WILLIAM A. TANNER, Am. J. M. Sc. **216**:258 (Sept.) 1948.

A study of five families in which poliomyelitis appeared provided evidence of a widespread distribution of virus in members of these households. There were 24 members in these households; 17 had poliomyelitis virus in their intestinal discharges; in 7 virus was detected in the throat. Poliomyelitis virus was detected in stool samples of 13 children and 4 adults. Virus was present in the throat of each of 5 children and 2 adults. On the basis of history of onset of illness and isolation of poliomyelitis virus in members of four households, it is suggested that virus was seeded in respective members at a common source.

HENSKE, Omaha.

POSTVACCINAL ENCEPHALITIS: A REPORT OF FORTY-FIVE CASES IN NEW YORK CITY. MORRIS GREENBERG and EMANUEL APPLEBAUM, Am. J. M. Sc. **216**:265 (Nov.) 1948.

Forty-five cases of encephalitis occurred in New York city in 1947 following the vaccination of about 5,000,000 persons, a case incidence of approximately 1 to 110,000 vaccinations. Four persons died. However, none of them showed postmortem lesions in the brain characteristic of postvaccinal encephalitis. The age distribution, pathologic aspects and etiologic basis of the disease are discussed.

HENSKE, Omaha.

A POSTVACCINIAL OCULAR SYNDROME. E. ROSEN, Am. J. Ophth. **31**:1443 (Nov.) 1948.

Rosen classifies the ocular complications of vaccination as those due to direct contact with a pustule and the indirect, delayed, secondary ocular complication which follows a definite incubation period. The author states that the latter resembles the encephalitic type of postvaccinal complication, in which the specific pathologic picture of perivascular myelinoclasis is likened to the vascular and perivascular ocular disturbance.

REESE [ARCH. OPHTH.].

THE USE OF POSITIVE PRESSURE AS AN AID IN THE HANDLING OF RESPIRATORY PARALYSIS FROM ANTERIOR POLIOMYELITIS. RICHARD MASLAND, R. B. LAWSON and W. M. KELSEY, J. Pediat. **36**:31 (Jan.) 1950.

Breathing against positive pressure resistance has been used before in the care of patients with poliomyelitis in conjunction with a tracheotomy. The authors suggest using the positive pressure respirator for patients with bulborespiratory poliomyelitis when tracheotomy has not been done. They recommend use of the positive pressure apparatus when moving patients from one tank type respirator to another or when the tank type respirator is opened for one reason or another. They also recommend the use of positive pressure in the treatment and prevention of pulmonary edema during the course of respiratory paralysis.

MACDONALD, Pittsburgh.

PURPURIC MANIFESTATIONS OCCURRING IN MEASLES IN CHILDHOOD. STEPHEN D. MILLS, J. Pediat. **36**:35 (Jan.) 1950.

Mills reports on a 6 year old boy in whom thrombocytopenic purpura developed ten days after the onset of measles. The boy later recovered completely. The complication is rare.

MACDONALD, Pittsburgh.

CLINICAL OBSERVATIONS ON THE USE OF AUREOMYCIN IN VARICELLA. M. M. MAZURSKY, LYDIA WRIGHT and MANFRED WEICHSEL, Pediatrics **5**:276 (Feb.) 1950.

Eighty-two patients between the ages of 6 months and 12 years with varicella whose rash was of less than twenty-four hours' duration and none of whose lesions were in the crust or scab stage were seen on admission and observed daily for six days. Forty-one of these patients received aureomycin orally (50 mg. per kilogram of body weight the first twenty-four hours and 25 mg. per kilogram the next forty-eight hours). Forty-one patients served as controls. Aureomycin had no effect on the patients treated. In 2 patients epidemic parotitis developed despite the administration of aureomycin early in the incubation period.

FROM THE AUTHORS' SUMMARY.

POLIOMYELITIS: EFFECT OF EXERTION DURING THE PRE-PARALYTIC STAGE. E. R. HARGREAVES, Brit. M. J. **2**:1021 (Dec. 11) 1948.

An analysis of 30 cases of poliomyelitis which occurred in Cornwall County, England, during 1947 and 1948 was made by Hargreaves in an effort to determine the effect on the ultimate prognosis of physical or mental exertion during the preparalytic stage of the disease. In agreement with a previous report by W. R. Russell in 1947, the present analysis revealed that severe physical activity during the preparalytic stage was associated with a grave prognosis, whereas only slight paralysis tended to develop in patients confined to bed during the preparalytic stage.

ECHOLS, New Orleans [ARCH. NEUROL. & PSYCHIAT.].

EPIDEMIOLOGIC AND CLINICAL COURSE OF A POLIOMYELITIS EPIDEMIC IN THE CHILDREN'S SPA ST. PETER-NORDSEE. G. BREITZKE, Med. Klin. **44**:16 (Jan. 7) 1949.

Twenty-nine children and adults with poliomyelitis were observed from May to September in a well isolated district. All were admitted to the hospital. Five of the patients died. Five others had severe paralytic manifestations. Four had slight paralysis. Fifteen patients recovered entirely. The possibility of contact infection could be excluded, and no 2 cases occurred in the same family, in spite of conditions favoring such an event. With regard to treatment it is stated that patients treated with convalescent serum in the preparalytic stage did much better than those not so treated. The serum was given in amounts of 10 cc. intraspinally and 10 cc. intramuscularly. The necessity to heat the serum to body temperature is stressed.

AMBERG, Rochester, Minn.

APPLICATION OF HONEY TO ELIMINATE DIPHTHERIA BACILLI IN THE CARRIER. H. DOLD and T. KNAPP, Med. Klin. **44**:243 (Feb. 25) 1949.

The smearing of honey with a smooth metal spatula three times a day on both tonsils with some force and the administration of fluid honey three times a day through both nostrils render swabs in two to two and a half weeks negative for

diphtheria bacilli (Stolte). It could be shown that natural honey inhibits the multiplication of diphtheria bacilli. Furthermore, the honey could transform them to pseudo diphtheria bacilli.

AMBERG, Rochester, Minn.

A RARE COMPLICATION OF MUMPS. ETTORE ROSSI, Helvet. paediat. acta **2**:103 (Jan.) 1947.

Rossi reports a case of parotitis epidemica in which the rare complication of parotitis purulenta bilateralis developed. Penicillin treatment led to rapid healing.

FROM THE AUTHOR'S SUMMARY.

EMBRYOPATHY FROM RUBELLA. A. FRANCESCHETTI, F. BAMATTER and J.-B. BOURQUIN, Helvet. paediat. acta **2**:339 (Aug.) 1947.

Franceschetti and associates report the first six cases observed on the European continent of congenital malformations in the newborn following rubella in the first third of pregnancy. The term "rubellar embryopathy" is suggested for describing these conditions. The following abnormalities of development have been noted: cataract, microphthalmos, microcephaly, pseudoretinitis pigmentosa, deafness, patent ductus arteriosus, dental malformations, pes valgus, hypospadias, ovarian cyst and ependymal pseudocyst. There is a comparison of the aforementioned cases with those of Anglo-Saxon authors. There also are notes regarding the pathogenesis of these fetal conditions and their prophylaxis and therapy.

FROM THE AUTHORS' SUMMARY.

CASE OF POSTSCARLATINA SPONDYLITIS. H. WISSLER, Helvet. paediat. acta **2**:371 (Aug.) 1947.

Wissler reports a case of spondylitis developing immediately after scarlet fever. The roentgenogram shows clear zones similar to cysts in the vertebrae and the transverse processes. Duration of the illness: one year.

FROM THE AUTHOR'S SUMMARY.

## Acute Infectious Diseases

RICKETTSIALPOX—A NEWLY RECOGNIZED RICKETTSIAL DISEASE: II. CLINICAL OBSERVATIONS. MORRIS GREENBERG, OTTAVIO PELLITTERI, IRVING F. KLEIN and ROBERT J. HUEBNER, J. A. M. A. **133**:901 (March 29) 1947.

The clinical features observed in 144 cases of rickettsialpox, a new disease of rickettsial origin, are described. It is characterized by the appearance of an initial lesion about a week before the onset of fever, chills, sweats, headache and backache, and by the appearance of a maculopapular and papulovesicular rash about three to four days after the onset of fever. Except for leukopenia, routine laboratory findings are generally negative. The usual bacterial agglutination tests are uniformly negative; however, antibodies for rickettsialpox are demonstrable by means of the complement fixation test. There have been no deaths.

FROM THE AUTHORS' SUMMARY.

RHEUMATIC FEVER: ITS RECOGNITION AND TREATMENT. GEORGE C. GRIFFITH, J. A. M. A. **133**:974 (April 5) 1947.

This is an over-all survey of a large group of patients of military age. Five per cent of the trainees had streptococcic infections of the upper respiratory tract

and in about 5 per cent of these the condition progressed to rheumatic fever. During the latent period of one to four weeks before the outbreak of the rheumatic fever, the painstaking physician will find some evidence of rheumatic infection. In the third phase of the disease, the active phase, rheumatic fever has protean manifestations. The syndromes are classified into four types of disease: acute fulminating type occurring in 4.3 per cent, subacute polycyclic type, in 27.6 per cent, subacute monocyclic type, in 61.3 per cent and subclinical type, in 5 per cent. Major and minor diagnostic criteria are reviewed. The importance of pneumonitis as secondary to carditis is emphasized because of its frequent occurrence and its causation of failure of the right side of the heart. Treatment included early recognition of the rheumatic state and institution of adequate general care and salicylate therapy. Sulfonamide treatment of the streptococcic infection did not prevent the subsequent development of rheumatic fever.

BAIRD, Wauwatosa, Wis.

ATYPICAL FEATURES OF RHEUMATIC FEVER IN YOUNG ADULTS. MAURICE SOKOLOW and ALBERT M. SNELL, J. A. M. A. **133**:981 (April 5) 1947.

Atypical clinical features of rheumatic fever in young adults include minimal presence or complete absence of articular symptoms, monarticular involvement, onset and major manifestations in hands and feet, prodromal aching for days and weeks prior to onset of acute arthritis, recurrent acute arthritis of short duration with apparently complete subsidence between attacks, absence of fever during the acute stage, atypical febrile course, association of rheumatic fever and Marie-Strümpell spondylitis, abdominal and precordial pain as the initial manifestation, onset with pericarditis and pneumonitis and subclinical recrudescence.

The most valuable criteria for the diagnosis in young adults were (1) arthralgia, (2) evidences of carditis, especially electrocardiographic changes (auriculoventricular block and inverted T waves), (3) fever and (4) persistent elevation of the sedimentation rate.

BAIRD, Wauwatosa, Wis.

RHEUMATIC BRAIN DISEASE: LATE SEQUEL OF RHEUMATIC FEVER. WALTER L. BRUETSCH, J. A. M. A. **134**:450 (May 31) 1947.

The author calls attention to the occurrence of rheumatic obliterating arteritis in about 5 per cent of patients in mental hospitals, a group that has combined rheumatic brain disease and rheumatic heart disease. The process involves chiefly the small meningeal and cortical vessels, producing gross or microscopic areas of softening. This is a late sequela of rheumatic fever and may occur from several months to many years after the acute stage of the disease.

BAIRD, Wauwatosa, Wis.

SOME RECENT EXPERIENCES WITH AMEBIASIS IN CHILDREN. MAUD LOEBER and JOSEPH S. D'ANTONI, New Orleans M. & S. J. **100**:276 (Dec.) 1947.

In four months of routine office practice, 73 cases of amebiasis were identified. Symptoms were more suggestive of a low grade systemic infection than of isolated intestinal disease. General features of these cases included changes in established bowel habits, appetite and personality. Nausea, vomiting, low grade fever, headaches, increased fatigability, weakness and frequent colds were common complaints. No constant physical findings were noted.

MCGUIGAN, EVANSTON, ILL.

TREATMENT OF MALARIA IN CHILDREN WITH CHLOROQUINE. T. L. NELSON and GERALD J. CONLIN, Pediatrics **5**:224 (Feb.) 1950.

Forty-nine children with 54 episodes of malaria were treated with chloroquine diphosphate under close hospital observation. Of these 54 episodes, 32 were due to Plasmodium vivax, 21 were due to Plasmodium falciparum and 1 was due to a mixed P. vivax and P. falciparum injection. Nine children severely ill with malaria responded well to this treatment. Only minor toxic effects of chloroquine were observed. Chloroquine in total doses of 0.5 Gm. (weight of chloroquine base) for infants 6 months old to 1.5 Gm. for persons 8 years of age or older is recommended as a rapid, safe and efficient drug for treatment of malaria in children.

FROM THE AUTHORS' SUMMARY.

THE TREATMENT OF ROCKY MOUNTAIN SPOTTED FEVER WITH PARA-AMINOBENZOIC ACID: A COMPREHENSIVE PLAN. SAMUEL F. RAVENEL, South. M. J. **40**:801 (Oct.) 1947.

The author points out the increasing incidence of this disease in the Middle West and the East, especially in the southeastern part of the United States. Six case reports of children who had spotted fever and recovered are included.

The author emphasizes the following points in discussing treatment: (1) restoration and maintenance of fluid and electrolyte balance by means of dextrose in sodium chloride solution or lactated Ringer's solution administered intravenously; (2) treatment of acidosis by appropriate intravenous and subcutaneous injections of sixth-molar lactate solution; (3) maintenance of serum protein level by the intravenous administration of blood plasma, serum albumin or blood; (4) high vitamin intake; (5) administration of paraaminobenzoic acid in a dose of 0.5 to 1 Gm. per pound (0.5 Kg.) of body weight per twenty-four hours. This is given orally in divided doses every two hours. It is buffered by administration in 10 cc. of 5 per cent sodium bicarbonate solution per gram of drug. A blood level of 30 to 60 mg. per hundred cubic centimeters should be achieved. Blood levels above 80 mg. per hundred cubic centimeters may prove hazardous. Administration of the drug is continued for four to five days after the fever subsides; (6) observation for untoward reactions to paraaminobenzoic acid: acidosis, leukopenia, abdominal distention and delirium; (7) observation for complications of spotted fever: congestive heart failure, pneumonia, encephalitis and thrombophlebitis. The heart failure is usually a reversible situation. (8) Hospitalization of patients with spotted fever for treatment.

LOGAN, Rochester, Minn.

THE ASPECTS OF HEMOGRAMS AND MYELOGRAMS IN VISCERAL LEISHMANIASIS AND ITS ASSOCIATION WITH MALARIA IN SARDINIAN BABIES. P. PINNA and S. FALCHI, Ann. ital. de Pediat. **2**:328 (Aug.) 1949.

Pinna and Falchi have studied the blood and the myelograms of 40 children with leishmaniasis and 18 children suffering from visceral leishmaniasis and malaria.

They think that the prevailing granulocytic leukopenia is due to a medullary defect in cell formation and cell evolution.

FROM THE AUTHORS' SUMMARY.

PRIMARY TUMORS OF THE BLADDER IN THE FIRST TWELVE YEARS OF LIFE WITH PARTICULAR ATTENTION TO BENIGN TUMORS. L. AMMANITI, Arch. ital. pediat. e. puericolt, **13**:181, 1949.

Ammaniti reports a case of a bladder polyp in a 16 month old child, who was operated on about five months after the onset of urinary troubles with extirpation of a tumor situated in the bladder neck.

Histologically there were represented in the tumor all the elements of the bladder walls, including the muscles, and there were also included two cysts covered with flat polystratified epithelium.

This child, who was dismissed from the clinic quite recovered from the operation after twenty days, was followed in the outpatient clinic for two and a half years. Since then he has not presented any urinary troubles and has always been in good health.

FROM THE AUTHOR'S SUMMARY.

AN EXTRAPYRAMIDAL POST-TETANUS SYNDROME. G. GASPARI, Clin. pediat. **30**:198 (March) 1948.

A boy 7 years of age had a typical attack of tetanus in February. He was hospitalized and discharged as cured in May after treatment with tetanus antitoxin. In July he again had the symptoms of tetanus and was given tetanus antitoxin with supplementary doses of tetanus anatoxin, but recovery was much slower and it was December before he was well again. It is the author's opinion that only one initial focus of infection existed; the production by the child of his own antibodies was insufficient to prevent the relapse.

HIGGINS, Boston.

GENERALIZED DERMAL INFILTRATION IN THE COURSE OF RHEUMATIC FEVER. ANTONIO PISANO, Arch. de pediat. d. Uruguay **21**:32 (Jan.) 1950.

A 9 year old child presented a slight pain in the right wrist and in both knees. A month later he had an intense pain in the left knee, without swelling and with a slight increase in temperature. Rheumatic fever was diagnosed and sodium salicylate was given in enteric-coated pills in a dose of 5 Gm. daily. As they were not well tolerated, they were replaced a few days later with aminopyrine (1.20 Gm. daily), use of which was continued for four months. A week from the beginning of the disease, a painless and nonpitty infiltration appeared in the skin of the face and neck, which extended to all the body, being more marked in the legs. It varied in intensity from day to day. It lasted almost one and a half months without changes; then it decreased and disappeared in the course of three months. The author considers the possibility of rheumatic, thyroid and allergic origin of the infiltration, tending to favor rheumatism as the cause.

FROM THE AUTHOR'S SUMMARY.

BANTI DISEASE AND ITS RELATION TO OCCULT MALARIA IN CHILDREN. A. ECKSTEIN, Ann. pædiat. **170**:113 (March) 1948.

The conception of "Banti's disease" has even today some justification as a clinical heading for all disorders that show splenomegaly and degeneration of splenic tissue, with replacement by connective tissue, and which cannot be classified within the group of specific diseases characterized by splenomegaly (malaria, kala-azar, cirrhosis, glycogenosis and Niemann-Pick disease). With further progress in diagnostic possibilities, it will be possible to limit the conception of "Banti's disease" and to replace this diagnosis by a well determined one of the aforementioned group.

An example of this kind is presented by 1 patient who was kept under clinical observation over a period of months. Numerous examinations of the blood and of sternal and splenic punctates, as well as constant control of temperature seemed to warrant, after exclusion of all the other illnesses which had to be considered, especially malaria and kala-azar, the diagnosis of "Banti's disease." In addition

to that the spleen, which on removal weighed 3,500 Gm., showed histologically only degeneration with proliferation of the connective tissue, while the characteristic signs of malaria (plasmodia and pigmentation) were absent.

Immediately after the operation the typical picture of tertian malaria (type of temperature curve; tertian ring forms) developed. Thus, it became clear that this was an occult form of malaria which had presented the picture of Banti's disease and which could not have been diagnosed previously in spite of all efforts. This observation again confirms the difficulties met in the diagnosis of occult malaria.

In spite of the splenectomy there were no complications, and the disease was cured eventually after several relapses. This corresponds with earlier observations that malaria in patients without a spleen is not bound to be particularly serious or, as some authors claim, fatal. Splenectomy is, therefore, justified in similar cases in which the diagnosis cannot be clearly established.

FROM THE AUTHOR'S SUMMARY.

PYRIFER TREATMENT OF TYPHOID: NEGATIVE EFFECT WITH PROTRACTED COURSE. HELMUT NEUMANN and EDGAR P. HOMMER, Med. Klin. **44**:343 (March 18) 1949.

The authors describe 2 patients with typhoid, treated with pyrifer (a mixture of nonpathogenic fever-producing bacteria), in whom, after a short drop of the fever, the condition became much worse and the disease lasted much longer than in 2 patients with similar conditions without pyrifer treatment. In other patients beneficial results were obtained with this treatment.

AMBERG, Rochester, Minn.

DEMONSTRATION OF OXYURIS WITH CELLOPHANE® ADHESIVE STRIPS. CARLA EBERT, Med. Klin. **44**:375 (March 25) 1949.

A cellophane® adhesive strip is placed over the anal region and left overnight. Of 250 children a positive result in 217 (87 per cent) was obtained with this method, as against 120 (48 per cent) with smears from the anal region.

AMBERG, Rochester, Minn.

OPERATION IN A CASE OF PULMONARY ECHINOCOCCOSIS. B. VOLTAY and G. GEDEON, Paediat. danub. **4**:46 (July) 1948.

After a survey of the pathologic and clinical aspects of hydatid disease, a case of pulmonary echinococcosis is presented. A girl 7 years of age suffered from loss of weight and frequent elevations in temperature for three years. Tomography revealed a circular shadow the size of an apple in the lower lobe of the left lung. The specific complement fixation test gave a negative reaction; there was severe anemia but no eosinophilia. Surgical removal was facilitated by the subpleural site of the cyst. After operation, interlobar pleurisy appeared, but recovery was uneventful. The reaction to the complement fixation test remained negative.

The authors recommend surgical removal in similar cases. Conservative treatment with the expectation of spontaneous rupture and evacuation of the cyst, as well as puncture, is considered out of date and dangerous. For the sake of early recognition, mass roentgenologic survey of the population exposed to infection is suggested.

FROM THE AUTHORS' SUMMARY.

## Chronic Infectious Diseases

TUBERCULOSIS IN CHILDHOOD. LLOYD B. DICKEY, California Med. **70**:171 (March) 1949.

Physicians who deal with children have much to contribute toward case finding in tuberculosis. The tuberculin test is the most accurate weapon at hand. Contacts other than the parents should be looked for. Symptoms to be noted, besides fever, are ocular and cutaneous complaints. In the physical examination the chest is relatively unimportant as compared with the eye, the skin and the lymphatic and skeletal systems. In the roentgenographic examination, epituberculosis and atelectasis should be differentiated. When gastric washings are necessary for the diagnosis, the tuberculin test on the guinea pig should not be forgotten. Careful laboratory studies will clear up roentgenographic confusion.

In the treatment, removal of contact is essential, and often all that is necessary, but other factors should be considered. Of the commoner complications, atelectasis, bronchiectasis and cavitation or reinfection may be treated surgically with all the accepted methods except thoracoplasty. Heliotherapy should not be forgotten in treatment of bone and joint tuberculosis. It is hoped that BCG will prove efficacious in vaccination, but published reports are not scientifically convincing. The vaccination destroys the value of the tuberculin test when used, and it should never be substituted for removal of contact as a prophylactic measure.

PRYOR, Redwood City, Calif.

ALLERGOMETRY IN TUBERCULOUS CHILDREN AS AFFECTED BY THE LOCATION AND BY THE REPETITION OF THE TUBERCULIN TEST. G. LODI, Clin. Pediat. **31**:198 (April) 1949.

Tuberculin tests made on the skin directly over an active tuberculous pulmonary or glandular lesion produce more intense reactions than do tests made on the skin of the symmetric part of the body, where there is no active lesion. However, where the tuberculous lesion is latent, the skin tuberculin reactions are of the same intensity on the two sides of the body.

HIGGINS, Boston.

PERFORATION OF BRONCHIAL NODES IN PRIMARY TUBERCULOSIS IN CHILDHOOD. T. VALLEDOR, J. C. MERIDA and A. GUERNICA, Rev. cubana de pediat. **19**:635 (Nov.) 1947.

The authors report on 8 patients with perforation of the bronchus from a tuberculous mediastinal node. This occurred in both white and Negro children. Six of the patients were under 1 year of age; 1 patient was 2 years and 1 was 10 years old. A diagnosis of fistula was confirmed by postmortem observations in 4 patients and by roentgenogram and bronchoscopy in 2; in the remaining 2 the diagnosis was on clinical basis only. There are photographs of the specimens obtained on the autopsy examination and reproductions of roentgenograms showing types of lesions. The 8 cases occurred in a series of 410 patients with primary tuberculous infections in the sanatorium in Habana, Cuba. The typical symptoms appear to be the sudden onset of coughing in a child, with an enlarged mediastinal shadow and febrile reaction, accompanied with expectoration, dyspnea, cyanosis and increased sweating.

KEITH, Rochester, Minn.

STREPTOMYCIN TREATMENT IN TUBERCULOSIS OF INFANCY AND CHILDHOOD. T. VALLEJOS, J. MIR and D. CAZAÑAS, Rev. cubana pediat. **21**:181 (April) 1949.

We summarize in this paper the results obtained with streptomycin in 44 tuberculous children treated at the Angel Aballi Sanatorium in Habana, Cuba, during the last two years. At the beginning of treatment 28 of the patients were under 3 years of age, 2 were 4 years old and 14 were between 10 and 14 years of age.

The disorders treated included meningitis, generalized miliary tuberculosis, oropharyngeal tuberculosis, ulcerative tracheobronchial tuberculosis, draining cutaneous sinuses, bone and joint tuberculosis and fibrocaseous and primary tuberculosis. The average duration of the treatment was two to four months; the daily doses were from 0.5 to 2 Gm., with an average of 1 Gm., divided into four intramuscular injections. The period of observation after treatment varied from two to seventeen months, with a mean of six to twelve months.

As a result of this treatment, 7 patients died (5 with meningitis). In 4, the condition remained unchanged; 8 improved considerably, and 25 are apparently cured at present. Only 5 presented secondary toxic symptoms: One had complete deafness, and 4 had a rapidly compensated vestibular disturbance.

The 14 patients treated for the primary disease included 4 with a gross primary complex, 4 with lobar or segmental infiltration, 2 with pneumonia and 3 with tuberculous bronchopneumonia, 1 having tuberculosis of the left testis as an added complication. All the patients were under 2 years of age and 6 were under 1 year. The average dose given these patients was 0.5 Gm., and the total dose was 15 to 60 Gm., with a period of observation of five to twelve months. Clinical recovery and roentgenologic regression, with return to a normal sedimentation rate, were observed in all patients.

In spite of the relatively high doses according to the body weight (average, 0.5 Gm.) used in our 14 patients with primary tuberculosis, no toxic manifestations were observed. It seems that infants and small children tolerate the drug much better than older patients.

We have often before expressed the importance of the use of streptomycin in the primary forms (evolutive) in infants, particularly in those under 3 years of age. With 2 goals in mind, we facilitate the involution of primary complex and prevent the generalization of the infection to the meninges that is so frequent in these early years.

Several facts favor this way of reasoning:

1. In the first three years of life tuberculous infection occurs less frequently, but the mortality rate is higher than at any other period during childhood. In accordance with Wallgren's figures, in the first year of life, mortality is ten times higher than after the third year, dropping from 5 to 0.5 per thousand afterward.

2. Miliary tuberculosis appears predominantly in the first year of life. In a series of 84 children reported on by Wallgren, 40 were observed during the first year and 20 during the second and third years. In other words, 60 of 84 cases occurred in the first three years of life. The same thing happens with tuberculous meningitis, which is frequent only during the first three years, comprising 70 to 80 per cent of the cases.

3. Miliary generalization and meningitis come about generally within the first three months after the first positive biologic reaction or in patients with a recent primary infection. From 176 patients with meningitis reported on by Wallgren, the disorder in 94.9 per cent coincided with a recent primary complex as detected by

clinical and roentgenologic examinations, and in only 5.1 per cent with a capsulated complex. In no patient did the meningitis occur after calcification of the complex.

4. Infantile tuberculosis due to various factors, intensive and repeated familial contagion, lack of acquired resistance, the development of the lymphatic system and the small volume of the body, evolves in some ways as the experimental infection in the guinea pig does, with a serious course and great tendency to dissemination. At this early age, meningitis occurs frequently following slight primary lesions detected only on roentgenogram. This is apparently the primitive meningitis of the French authors.

5. During the first months after the primary complex, the bacillemia occurs systematically in patients at all ages; but in infancy the optimal condition is present, so that the blood dissemination culminates in a miliary spread or meningitis.

On the other hand, it is in the blood stream and in recent, highly vascularized lesions that the bacteriostatic action of the antibiotic is greater. It is logical to suppose that during this phase the streptomycin is able to avert the spreading by diminishing the virulence of the germs and facilitating their destruction and elimination, which, at the same time, favors the more rapid involution of the primary complex.

Based on the aforementioned statements, we consider that streptomycin should be administered in a prophylactic form in every active primary infection in patients under 3 years of age. In this respect, the temperature curve, the follow-up roentgenogram and the sedimentation rate are important factors in the decision of when to start treatment and in subsequent management. The use of streptomycin does not exclude the importance of and the benefits from sanatorium treatment and the isolation of the patients from the contaminated environment.

We believe that in the near future, when the production cost of this drug shall be reduced and its use generalized, mortality due to tuberculosis in children will drop considerably.

FROM THE AUTHORS' SUMMARY.

PROGNOSTIC SIGNIFICANCE OF CADMIUM REACTION IN BLOOD SERUM FOR THE COURSE OF PULMONARY TUBERCULOSIS AS COMPARED WITH OTHER LABILITY REACTIONS. A. PEDRAZZINI, G. ROSSI and F. WUHRMANN, Schweiz. med. Wchnschr. **79**:289 (April 2) 1949.

To 0.4 cc. of fresh serum taken before breakfast, 0.2 cc. of a 0.4 per cent cadmium sulfate solution is added. If turbidity occurs, it is graded 2 plus and 1 plus. A strongly positive persistent reaction is associated with a bad prognosis. A negative reaction, particularly if persistent, indicates relatively benign pulmonary tuberculosis.

AMBERG, Rochester, Minn.

THERAPY OF TUBERCULOSIS WITH PARA-AMINOSALICYLIC ACID, WITH SPECIAL REFERENCE TO BRONCHIAL AND RENAL TUBERCULOSIS. R. HUG, S. MOESCHLIN and E. TANNER, Schweiz. med. Wchnschr. **79**:353 (April 23) 1949.

Five patients with tracheobronchial tuberculosis were treated with para-aminosalicylic acid with beneficial results even when the condition was streptomycin resistant. In 9 of 12 patients with renal tuberculosis the concomitant tuberculosis of the urinary passages responded well.

AMBERG, Rochester, Minn.

DIAGNOSTIC, PROGNOSTIC AND PROPHYLACTIC PROBLEMS IN TUBERCULOSIS OF CHILDREN. KARL KUNDRATITZ, Wien. klin. Wchnschr. **61**:217 (April 8) 1949.

This is a postgraduate lecture. It emphasizes that careful observation of the reactions to repeated tuberculin tests can give information beyond simply positive or negative results, particularly with regard to the state of immunity. The various methods of eliciting the tuberculin reaction are discussed briefly. Attention is called to the initial fever four to eight weeks after infection and the exanthems occurring about two months after infection. Erythema nodosum as a tuberculo-allergic phenomenon is discussed. The results of clinical and roentgenologic examinations are given briefly, also the sedimentation rate and the morphologic blood picture. The allergometry of Groer has given aid in prognosis. On symmetric places of the back intracutaneous tuberculin injections of various concentrations are given. The relation of concentration and diameter of reaction is considered. Roughly speaking, when the reaction with greater dilutions remains relatively strong, a less benign course is indicated. With reference to prophylaxis, protection against infection is regarded as desirable, since first infection in later life is only exceptionally responsible for a malignant course of the tuberculosis. The beneficial results of BCG vaccination are considered proved. Favorable hygienic conditions, including proper nutrition, are considered of prophylactic value.

AMBERG, Rochester, Minn.

CHORIORETINITIS DUE TO TOXOPLASMA. F. BAMATTER, Ophthalmologica **114**:340 (Oct.-Nov.) 1947.

A case of leptomeningitis due to Toxoplasma in a newborn infant is described. The condition was associated with hydrocephalus and macular chorioretinitis. Toxoplasmas were observed in histologic sections of the brain and retina. The mother of the child had a cat which died of an unknown disease shortly before the baby was born. The mother had multiple scratches on her legs caused by the cat. The author is of the opinion that the Toxoplasma is transmitted from house pets by ticks or fleas. Excellent illustrations accompany the article.

KIRBER [ARCH. OPHTH.].

HAS BCG VACCINATION ANY INFLUENCE ON THE GENERAL HEALTH AND DEVELOPMENT OF INFANTS? ARNE K. LARSEN and POUL BASTRU-MADSEN, Nord. med. (Hospitalstid.) **33**:472 (Feb. 21) 1947.

The increase in body weight of 22 infants at an infants' home vaccinated with BCG shortly after birth and given cow's milk mixtures during the first eight to twelve weeks corresponded to that of 100 nonvaccinated infants fed in the same way kept at the same infants' home. All the vaccinated infants gave positive reactions to tuberculin after eight weeks, and none displayed any signs of illness during the stay in the infants' home.

WALLGREN, Stockholm, Sweden.

TUBERCULOSIS OF THE CONJUNCTIVA. BJÖRN FOSS. Nord. med. (Norsk mag. f. lægevidensk.) **33**:690 (March 14) 1947.

Four patients with tuberculosis of the conjunctiva are reported on. One was a boy 10 years of age. The diagnosis on his admission to the hospital was tumor of the parotid gland. There were edema of the left eyelid, hypertrophic conjunctivitis with ulceration and pinhead nodules, enlargement and abscess of the preauricular lymph nodes, and a positive tuberculin reaction. Otherwise, there were no signs of tuberculosis.

WALLGREN, Stockholm, Sweden.

NECESSITY FOR EXAMINATION OF CEREBROSPINAL FLUID IN TREATMENT OF BABIES WITH CONGENITAL SYPHILIS. C. GOEDHART, Nederl. tijdschr. v. geneesk. **93**:25 (Jan. 1) 1949.

In the numerous articles published during recent years on the treatment of congenital syphilis, only sporadically has examination of the cerebrospinal fluid been mentioned. A positive Wassermann reaction in the spinal fluid proves the existence of chronic syphilitic meningitis, causing permeability of the brain and the choroid plexus to syphilitic reagins. This meningitis may have a latent course, but later on it may cause severe bodily and/or psychic disturbances. When the other clinical signs of congenital syphilis have disappeared, a positive Wassermann reaction in the spinal fluid proves that the child is not yet cured. It is recommended that an examination of the spinal fluid be done during and after the treatment of congenital syphilis.

VAN CREVELD, Amsterdam, Netherlands.

## Diseases of Blood, Heart and Blood Vessels and Spleen

THE DIAGNOSIS OF CONGENITAL ANEURYSM OF THE PULMONARY ARTERY. CHARLES T. DOTTER and ISRAEL STEINBERG, New England J. Med. **240**:51 (Jan. 13) 1949.

The authors distinguish congenital aneurysm of the pulmonary artery from dilatation and aneurysm of that structure due to other causes. Of 650 angiocardiographic studies, 2 were considered as representing congenital aneurysm of the pulmonary artery and these are reported in detail.

The importance of cardiac catheterization, pressure studies and angiocardiography in the delineation of this lesion is emphasized. Surgical intervention is not indicated.

WHEELOCK, Denver.

MULTIPLE SITES FOR BONE-MARROW PUNCTURE, WITH PARTICULAR REFERENCE TO CHILDREN. JACK J. RHEINGOLD, LOUIS WEISUSE and WILLIAM DAMESHEK, New England J. Med. **240**:54 (Jan. 13) 1949.

Examination of bone marrow in hematologic disease has long been done only on sternal marrow. The authors are of the opinion that multiple puncture sites are valuable and they have utilized the vertebral spinous process and the iliac crests of adults and children with success. The methods and results of this approach are described. Among the advantages listed are: facility in following the course of the disease or effect of therapy; confirmation of marrow diagnosis; the securing of additional data, and the opportunity to obtain diagnostic material when the sternal marrow is not available or is unsatisfactory because of the density of abnormal cellular components.

WHEELOCK, Denver.

WOLFF-PARKINSON-WHITE SYNDROME WITH CONGENITAL HEART DISEASE. ESTELLE E. KLEIBER, Pediatrics **4**:210 (Aug.) 1949.

The Wolff-Parkinson-White syndrome, consisting of a shortened P-R interval associated with a widened QRS complex as an anomaly of the conduction system of the heart, has long been recognized in the adult. It has been reported oftenest in young, apparently healthy and normal adults who are, however, susceptible to attacks of paroxysmal tachycardia. A few cases of this syndrome have been noted in children in association with congenital heart disease. This paper presents such a case of a child who had his first episode of paroxysmal tachycardia at the age of 7 months and then remained symptomless until 6 years of age. Physical activity

at school then precipitated more frequent attacks. Investigation at this time revealed probable congenital heart disease and a typical electrocardiogram. Several other cases of young children are cited. FROM THE AUTHOR'S SUMMARY.

EFFECTS OF CONTINUOUS RADIATION ON CHICK EMBRYOS AND DEVELOPING CHICKS: II. BONE MARROW, LYMPHOID TISSUE AND PERIPHERAL BLOOD. SHIELDS WARREN and FRANK J. DIXON, Radiology **52**:869 (June) 1949.

Inhibition of maturation of hematopoietic cells and reduced mitotic activity resulted from irradiation by $P^{32}$ in small doses. Immediate cessation of the process with a fatal anemia resulted after large doses. These changes later were reversible in nonfatal cases. The lymphoid tissue of the thymus was sensitive and showed a prompt reduction in mitotic activity which lasted until the retained $P^{32}$ had been concentrated in the bones. In peripheral blood, the lymphocyte count fell first and recovered before that of the other cell types. The granulocyte count fell next most rapidly and recovered most slowly. The red cell count fell most slowly but returned to normal more rapidly than the granulocyte count.

ANSPACH, Chicago.

RADIOCARDIOGRAPHY: A NEW METHOD FOR STUDYING THE BLOOD FLOW THROUGH THE CHAMBERS OF THE HEART IN HUMAN BEINGS. M. PRINZMETAL, E. CORDAY, H. C. BERGMAN, L. SCHWARTZ and R. J. SPRITZLER, Science **108**:340 (Sept. 24) 1948.

A novel method for studying the passage of a bolus through the heart is described. Radioactive sodium, in tracer amounts, is injected into an antecubital vein, and the concentration of this material within the heart is determined by a Geiger-Müller counter placed over the precordium. An ink-writing device makes a permanent record of the time-concentration curve of radioactive sodium within the precordial area. In normal hearts two maxima are observed, representing the presence of the bolus in the right and left sides of the heart, respectively, at 3.5 and 9.5 seconds following the injection. After approximately 17 seconds, the curve becomes flat, indicating that the injected sodium has passed on to the systemic circulation. The slower circulation in the diseased heart is shown by a curve which is much flatter and longer (35 seconds). The left ventricular maximum is short or absent in cases of tetralogy of Fallot, because of the shunting of blood from the right side of the heart to the systemic circulation.

FORBES, St. Louis.

SURGICAL TREATMENT OF PATENT DUCTUS ARTERIOSUS. ROSS ROBERTSON, Canad. M. A. J. **60**:595 (June) 1949.

Eleven patients with patent ductus arteriosus were operated on with no deaths. The author discusses the indications and technic used; he favors the Gross method.

MCGUIGAN, Evanston, Ill.

MEGALOBLASTIC ANAEMIA OF INFANCY—THE DIFFERENTIAL DIAGNOSIS. M. MEDALIE, South African M. J. **23**:431 (May 28) 1949.

The recently described syndrome of megaloblastic anemia is described in detail. Diagnosis sometimes involves consideration of all causes of disturbance in red

cell maturation, blood destruction, hemopoietic aplasia, disturbance in hemoglobin synthesis and loss of blood. These points are covered briefly from the point of view of differential diagnosis.

McGUIGAN, Evanston, Ill.

NUMBER OF MEGAKARYOCYTES IN THE BONE MARROW OF CHILDREN. E. GRASSO and C. STICCA, Minerva pediat. **1**:26 (Jan.) 1949.

Counts were made of the total number of nucleated cells and of megakaryocytes per cubic millimeter in the fluid obtained on sternal punctures from 10 normal children, 2 months to 11 years of age. The number of megakaryocytes per 100 nucleated cells varied from 0.02 to 0.08, the mean ratio being 0.05; such variations as occurred between children were not related to the age of the child. One child with hemorrhagic purpura had a high ratio of 0.10, and two children with familial erythroblastic (Cooley's) anemia each had low ratios of 0.004.

HIGGINS, Boston.

HAND-SCHÜLLER-CHRISTIAN DISEASE. F. TOSCANO, Minerva pediat. **1**:37 (Jan.) 1949.

The case history of a girl born in 1934 is given from the time of the onset of symptoms in 1938 up to 1947. She had been under the care of the Pediatric Clinic in Novara, Italy, during this period. In 1939, she showed striking symptoms and signs of Hand-Schüller-Christian disease, having stunted growth, exophthalmos, prominent changes in the cranial bones on roentgenograms, diminished hearing and diabetes insipidus; her blood cholesterol was 590 mg. per hundred cubic centimeters. In 1947, she was a bit under normal height and slightly obese and showed none of the changes of puberty; she was deaf, had no signs of diabetes insipidus and had slightly enlarged spleen and liver. Some osteoporosis of the bones of the skull was the only bony abnormality seen on roentgenograms. Her blood cholesterol was 190 mg. per hundred cubic centimeters; she still showed exophthalmos.

HIGGINS, Boston.

LYSOZYMATIC POTENCY OF BLOOD SERUM OF NORMAL CHILDREN AND OF CHILDREN WITH SOME INFECTIOUS DISEASE. B. FIANDACA and M. A. DI CHRISTINA, Pediatria **57**:41 (Jan.) 1949.

With the use of the method of Caselli, the lysozymatic potency of the blood serums of 50 normal children, 2 to 12 years of age, was observed. The maximum dilution in which lysis occurred was 1:32 or 1:64 in 33 children; in 9 it was 1:16, and in 8 it was 1:128. Similar observations on the serums of 50 children with diphtheria, meningitis, poliomyelitis, typhoid, kala-azar or brucellosis showed a lower potency, the dilution in no child being greater than 1:16 during the illness; in only 55 per cent of the children was the dilution as high as 1:32 after the child had recovered from the illness.

HIGGINS, Boston.

CONGENITAL AREGENERATIVE ANEMIA. T. HALBERTSMA, Maandschr. v. kindergeneesk. **16**:432, 1949.

A description of congenital aregenerative anemia and a report on a patient who died of it, with the observations at autopsy, are given. The main symptoms of the disease are a severe normochromic and normocytic anemia with leukopenia, neutropenia and thrombopenia; no reticulocytosis is present. There is no connection with

syphilis or the Rh factor. The anemia begins two months after birth. A bone marrow study reveals no important changes. The only effective therapy is the transfusion of whole blood. This measure, however, must be repeated frequently and leads to brown pigmentation of the skin.

The patient described was a girl and the first child of the family. The anemia was detected at the age of 6 weeks. There were normochromic anemia and leukopenia, but no thrombopenia. Differential counts showed neutropenia and lymphocytosis. The child was treated with iron and liver, but no benefit was obtained from this therapy. Then repeated transfusions of whole blood were given. The child died at the age of 2½ years following a transfusion given while she was under anesthesia. The postmortem examination showed a hyperplastic bone marrow without fatty cells. Further observations were pallor of the tissues and hemosiderosis. The spleen had a normal structure and was poor in iron. The author prefers the name aregenerative anemia for this disease.

VAN CREVELD, Amsterdam, Netherlands.

CONGENITAL COMPLETE HEART BLOCK. H. P. J. KOENEN, Maandschr. v. kindergeneesk. **16**:444, 1949.

Congenital complete heart block in a man 22 years of age is described. When 9 months old, he had a pulse rate of 56, a loud systolic murmur in the third intercostal space and a loud second pulmonary sound. With the electrocardiographic findings the diagnosis of Roger's disease was made. The patient never had had any illness which may have offered an explanation for the changes in the heart. At the age of 22 years the man had not a single subjective symptom and he was able to work normally. The ventricular frequency was 48 and the atrial frequency 66. The roentgenogram showed that the heart was somewhat enlarged to the right and to the left. On auscultation the same symptoms were found as formerly, including a soft diastolic souffle on the pulmonary valve. The good condition of this patient with such severe changes of the heart is remarkable.

VAN CREVELD, Amsterdam, Netherlands.

CARDIAC HYPERTROPHY OF UNKNOWN ORIGIN. O. A. DRIESSEN, Maandschr. v. kindergeneesk. **16**:460, 1949.

A girl 8 months of age had an enlarged heart, especially to the left side, and a somewhat enlarged liver. The parents were healthy. At each intercurrent infection the child showed symptoms of an acute cardiac insufficiency; the liver then reached to a handbreadth below the costal margin. The electrocardiogram showed small deflections, while the tops of the T waves were nearly invisible.

The author made the diagnosis of cardiac hypertrophy of unknown cause, after having excluded all other causes for an enlargement of the heart, such as glycogenosis, so-called idiopathic hypertrophy of the heart, the pseudoidiopathic group with changes in the myocardium and the morbid picture of the abnormal origin of the left coronary artery from the pulmonary artery (Taussig).

VAN CREVELD, Amsterdam, Netherlands.

MALIGNANT UNIFORM LEUKOSIS. S. SANDKÜHLER, Med. Klin. **44**:42 (Jan. 14) 1949.

It is stated that the disease here described is not too rare and occurs mainly in childhood. The case of a 5 year old boy is described. The condition is to be distinguished from the leukemias. It is impossible to classify these disorders under

the headings of either lymphatic or myeloid leukemia. In the blood picture undifferentiated small round cells form the characteristic feature. It is assumed that they represent primitive degenerated reticular derivatives. The spleen and lymph nodes are enlarged. There is a tendency to localize tumor formation and cutaneous infiltration. Later in the course, the duration of which averages six months, an insufficiency of the myeloid cells is seen. It is not a septic disease but a tumorizing process, although it cannot always be designated directly as a sarcoma.

AMBERG, Rochester, Minn.

ACUTE INFECTIOUS LYMPHOCYTOSIS. F. HENI and E. ZEH, Med. Klin. **44**:75 (Jan. 21) 1949.

A girl 15 years of age became ill and showed a blood picture as described in cases of infectious lymphocytosis. The differential diagnosis from infectious mononucleosis is discussed. It may be mentioned that both occur predominantly in children and young adults. The authors are of the opinion that a differentiation is quite difficult.

AMBERG, Rochester, Minn.

CLINICAL SIGNIFICANCE OF CONTINUOUS RETICULOCYTE COUNTS IN THE TREATMENT OF ANEMIA. P. BÜCHMANN and R. H. RUDER, Med. Klin. **44**:102 (Jan. 28) 1949.

A new method for counting reticulocytes is given. With a blood sugar pipet 0.1 cc. of 1 per cent brilliant cresyl blue in Ringer's solution is measured into a small test tube with 0.1 cc. blood. After standing three to four hours in the cotton-stoppered tube, a drop is spread on a well defatted slide and the number of reticulocytes per 1000 erythrocytes are counted. Under liver therapy in cases of pernicious anemia a maximal increase in reticulocytes from 150 to 350 per thousand was noted (normal value, 5 to 12 per thousand), whereas anemia due to deficiency in iron responded to iron therapy with an increase to 34 to 82 per thousand.

AMBERG, Rochester, Minn.

DETERMINATION OF RED BLOOD CELL COUNT BY PHOTOELECTRIC COLORIMETER. J. H. P. JONXIS, Nederl. tijdschr. v. geneesk. **92**:2024 (July 3) 1948; **93**:102 (Jan. 8) 1949.

For routine examination a quick and reliable method for determination of the erythrocyte count was required. This method is based on the measurement of the turbidity of a highly diluted suspension of erythrocytes. In such a suspension the light absorption depends on the number of suspended particles, the size of the particles, the amount of hemoglobin and the amount of other dye substances present in the blood.

Fifty cubic millimeters of blood is suspended in 10 cc. of 2.5 per cent solution of sodium chloride, then the extinction is determined by means of a photoelectric colorimeter with a wavelength of 650 millimicrons. At this wavelength the hemoglobin absorbs almost no light. Only when severe icterus is present do mistakes arise. The influence of the diameter of the erythrocytes is suppressed by wrinkling them in the hypertonic sodium chloride solution.

A number of determinations for normal persons was performed, and the results were presented in a graph, on the horizontal axis of which the number of erythrocytes was indicated and on the vertical axis the value found for the extinction. It appeared that the extinction was directly proportional to the erythrocyte count,

and in the curve the erythrocyte count could be directly read. This method can be used only when the diameter of the erythrocytes is about normal. When the color index is larger than 1, the erythrocyte count is found to be too large; when it is smaller than 1, this count is too small, so that a correction is necessary. There appears to exist a systematic relation between the color index as derived from the number of counted erythrocytes and the color index as derived from the number of erythrocytes determined by means of the colorimetric method. This relation was fixed in a graph by means of a large number of determinations in patients with greatly varying color indexes. By means of this curve it is possible to obtain for each colorimetric number the associated real color index, and then by means of the value for hemoglobin content it is easy to find the real number of erythrocytes. The author does not mention his method for the determination of the hemoglobin content.

VAN CREVELD, Amsterdam, Netherlands.

## Diseases of Nose, Throat and Ear

PSEUDOMEMBRANOUS INFLUENZAL LARYNGOTRACHEOBRONCHITIS. P. PENIAZKA, Pediat. listy **3**:192, 1948.

On the basis of 8 cases, the clinical and bacteriologic findings and the therapy of the disease are discussed. The inspiratory and expiratory stridor was striking. There was no aphonia; pulmonary complications were frequent. The bacterial flora was mixed. The possibility of diphtheria was excluded. The treatment was conservative; intubation and tracheotomy were performed only for threatened asphyxia.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF SUBACUTE OTITIS BY PENICILLIN GIVEN INTRATYMPANICALLY. D. KOLLÁR, Paediat. danub. **3**:87 (Feb.) 1948.

Encouraging results were achieved by the injection of penicillin solution into the tympanic cavity in patients with subacute otitis caused by penicillin-sensitive organisms. The injections were given with thin, short-edged needles. Two-tenths to 0.3 cc. of a penicillin solution, i. e., 2,000 to 3,000 units, was administered.

The method is not indicated in the acute stage of otitis media, partly because it is not possible to inject anything into the tympanic cavity, this being compressed to a narrow gap by the congested mucous membranes, and partly because most of the processes respond well to sulfonamide treatment alone. In patients with chronic conditions in which the osseous cells are not involved, a gauze strip soaked in penicillin should be applied. As this method is not efficacious in either acute or chronic cases with bone involvement, it may facilitate the diagnosis of mastoidal processes. In all the patients treated with intratympanic injection complete restoration took place in a short time.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF SINUSITIS IN INFANTS. E. GYÖRGY, Paediat. danub. **3**:97 (Feb.) 1948.

The pathogenesis of paranasal sinusitis and involvement of the maxilla has not yet been settled. Some authors hold the view that an acute osteomyelitis of the maxilla must be responsible for the condition, whereas others regard empyema of the maxillary sinus as the primary factor. Infection may spread from the nasal cavity to the maxillary sinus either through the mucous membrane or through the dense capillary network of the thin, porous bones.

In the former case, facial sinusitis may occur without maxillary osteomyelitis. In the latter case, however, when infection is propagated through the bones, osteomyelitis of the maxilla is always present and the involvement of the facial sinus occurs only afterward.

The tooth buds may also become involved in this process. While the nasal route is the common way in which tooth germs become infected, hematogenous infections also occur. Conditions involving the bone and the tooth germs occur almost without exception in the alveolar processes of the upper jaw. This proves that infection is usually of nasal origin.

An account is given of 22 patients. Of these, 14 were observed before penicillin became available. Among them 8 died, 2 improved and only 4 recovered. The sinus had to be opened in 7; abscesses occurred in 4, and only 2 were not operated on. Eight infants were treated with penicillin. Of these, none died, 3 were discharged improved and 5 recovered. Opening of the facial sinus and of the ethmoidal cells had to be done in 4, and abscesses were opened in 2 children; the rest recovered without operative measures. The method used for opening the facial sinus was that of Caldwell and Luc. The sinus was irrigated with penicillin solution once daily for several days. Recovery was always complete within a few days.

FROM THE AUTHOR'S SUMMARY.

SULFANILAMIDE IN THE TREATMENT OF TONSILLITIS. H. A. VOET, Nederl. tijdschr. v. geneesk. **92**:1380 (May 8) 1948.

In the hospital of the University at Basel, Switzerland, a comparison was made between a group of patients with uncomplicated tonsillitis treated during the period 1936 to 1940 and a group of patients admitted from 1941 to 1945, when sulfanilamide was administered.

This investigation was possible because in Switzerland patients with tonsillitis are hospitalized when sufficient help at home is not available. Six grams of "elkosine" (sulfamethazine) was given in twenty-four hours. This treatment did not shorten the course of the disease. The period of fever was scarcely influenced. Most investigators confirm these results. Voet warns against the use of sulfanilamide in tonsillitis. The occurrence of complications is not reduced. Apart from the toxicity of the drug and the possibility of allergy which will handicap treatment in the future, it is pointed out that a too frequent administration of sulfanilamide may give rise to the development of chemoresistant bacteria.

VAN CREVELD, Amsterdam, Netherlands.

## Diseases of Lungs, Pleura and Mediastinum

THE CONTROL OF EXPERIMENTAL PNEUMONIA WITH PENICILLIN. CATHERINE B. WILSON, STANLEY H. DURLACHER and ELEANOR A. BLISS, J. Pharmacol. & Exper. Therap. **95**: 509 (Jan.-April) 1949.

The authors previously showed that penicillin by inhalation was as effective as by injection in treatment of lobar pneumonia in rats; also the penicillin blood level was about the same by the two methods. In the present paper they report that the mortality in pneumococcic pneumonia of 24 hours' duration in rats was somewhat less than half when penicillin was administered by the inhalation method than when is was administered by injection. Other data, such as the concentration of penicillin in the pneumonic and the free lung areas in the pneumonic rats and in uninfected rats, are presented.

PILCHER, Cleveland.

ATTEMPTS TO CURE INFANTILE ASTHMA WITH PREPARATIONS FROM URINE OF PREGNANT WOMEN. P. BRUSA, Lattante **20**: 1 (Jan.) 1949.

Callegari, of the Serum Therapy Institute of Milan, has prepared a substance (substance C) from the urine of pregnant women; it has the antispasmodic factor, which has been noted in commercial preparations, but the gonadotropic factor has been removed. Brusa reports some clinical observations in which this substance C has been given to five asthmatic children, several of whom also had eczema. Very satisfactory and lasting benefits followed its injection in four of the patients. A severe asthmatic attack developed in the fifth child after the first injection; it seemed advisable to discontinue its use with this child.

HIGGINS, Boston.

A SIMPLE AND PRACTICAL TECHNIC FOR BRONCHOGRAPHY IN INFANTS. G. DETONI, V. B. BORI and F. G. PAPIO, Minerva pediat. **1**: 285 (Aug.) 1949.

An O'Dwyer intubation tube is used for the intratracheal administration of an iodized oil. An accessory tube extends from the mouth through the O'Dwyer tube; the oil is injected by a syringe through this tube.

HIGGINS, Boston.

AEROSOL THERAPY OF INFLUENZAL ASTHMATIC BRONCHITIS IN TUBERCULOUS PATIENTS. F. COPELLO and A. GHIO, Pediatria **57**: 514 (July) 1949.

More rapid relief of an infectious asthmatic bronchitis was obtained by the use of penicillin and an antispasmodic drug than by the aerosol method and than when penicillin was given by parenteral injections.

HIGGINS, Boston.

AEROSOLS IN PEDIATRICS. CARLOS ALBERTO BAUZA, Arch. de pediat. d. Uruguay **20**: 86 (Feb.) 1949.

The author summarizes the experimental foundations of aerosol therapy with chemotherapeutic drugs and antibiotics in the treatment of bronchopulmonary infections. The physical properties of penicillin aerosol suggest that it is the method of choice for treating bronchopulmonary infections caused by bacteria sensitive to penicillin. The technic, which is detailed, is innocuous and easy. The author reports the results of treatment in one patient with acute lung abscess, three with bronchiectasis and three with bronchopneumonia treated with penicillin aerosol alone or alternatively with azasulfamide aerosol.

FROM THE AUTHOR'S SUMMARY.

ATYPICAL PRIMARY PNEUMONIA IN INFANCY. R. VALDEZ DIAZ, JOSE D. ROUSSELOT, RENE MONTERO and PAUL PEREIRAS, Rev. cubana de pediat. **20**: 503 (Sept.) 1948.

The authors studied 20 children of different ages with atypical primary pneumonia. Most investigators agree that the etiologic agent is a virus. The pathologic lesions are consistent and characteristic, but the clinical picture is not characteristic. While various laboratory aids are of help in diagnosis, the roentgenogram is the most valuable. The prognosis is usually good, and there is no specific treatment, although administration of sulfonamides and antibiotics is advisable to avoid complications.

KEITH, Rochester, Minn.

PULMONARY INSUFFICIENCY. HANS-OLOF MOSSBERG, Acta paediat. 1949, supp. 75, p. 187.

A case of pulmonary insufficiency in a girl of 11 with pulmonary fibrosis and pronounced clubbing of the digits is described. The pulmonary function was investigated according to the method of Cournand and Richards. Necropsy confirmed the diagnosis of interstitial pulmonary fibrosis. The case illustrates the symptomatic similarity between cardiac and pulmonary insufficiency with dyspnea and cyanosis and also the present means of analysis and specific diagnosis.

FROM THE AUTHOR'S SUMMARY.

## Diseases of the Gastrointestinal Tract, Liver and Peritoneum

PERITONEOPERICARDIAL DIAPHRAGMATIC HERNIA: REPORT OF A CASE IN A NEWBORN INFANT SUCCESSFULLY CORRECTED BY SURGICAL OPERATION WITH RECOVERY OF THE PATIENT. ANGUS K. WILSON, WILLIAM R. RUMEL and O. L. ROSS, Am. J. Roentgenol. **57**:42 (Jan.) 1947.

The authors found 8 previous cases of this rare condition reported in the literature. In 2 operation was performed but the patients failed to survive. The child reported on here survived the repair, but nine months after the operation a check-up examination disclosed a recurrence of diaphragmatic herniation, with much of the small intestine above the diaphragm. A second repair will be attempted.

The authors point out that, clinically, the condition cannot be distinguished from the commoner peritoneopleural diaphragmatic hernias. However, postprandial cyanosis relieved by vomiting suggests the possibility of peritoneopericardial herniation.

HARRISON, Chicago.

DUPLICATIONS OF THE ALIMENTARY TRACT. EDWARD J. DONOVAN and THOMAS V. SANTULLI, Ann. Surg. **126**:289 (Sept.) 1947.

Duplications of the alimentary tract are usually discovered in infancy and childhood. They are observed more commonly in boys. They are of clinical importance because of the serious symptoms which they may produce. No characteristic symptoms are caused by this anomaly, but duplications of the alimentary tract should always be considered in the differential diagnosis of massive intestinal hemorrhage in patients of the younger age group.

With proper preoperative care, resection or excision of these anomalies can be performed with complete relief of symptoms. Six cases are reported.

BANTIN, Omaha.

HAMARTOMA OF THE LIVER. ROBERT J. PATTON, Ann. Surg. **127**:180 (Jan.) 1948.

Hamartoma of the liver is a structurally variable but benign and resectable tumor which occurs predominantly in infants. The tumor is congenital; it is more or less encapsulated, does not contain mitotic figures and does not metastasize. Surgical treatment offers a good prognosis if the growth is totally removed. The author reports 1 case.

BANTIN, Omaha.

A New Method of Restoring Continuity of the Alimentary Canal in Cases of Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula Not Treated by Immediate Primary Anastomosis. Richard H. Sweet, Ann. Surg. **127**:757 (April) 1948.

The author describes a one stage operation to be used in cases of congenital atresia of the esophagus in which the esophagus is too short to do a closure of the fistula followed by the performance of a primary anastomosis. He gives in detail the three steps of the procedure.

During the postoperative period, the author stresses the use of solutions intravenously for seven to ten days. After five to seven days, administration of fluids by mouth is allowed. By the end of twelve to fourteen days, the child should be able to take a diet suitable for his age. Penicillin is administered until the danger of postoperative sepsis and pulmonary complications is over (approximately one week). The child should be kept in an oxygen tent for a few days.

Bantin, Omaha.

Lymphangioma of the Mesentery. G. V. Brindley and G. V. Brindley Jr., Ann. Surg. **127**:907 (May) 1948.

Benign tumors of the mesentery occur rarely and lymphangiomas in this location are especially unusual. Most writers favor the opinion that lymphangiomas arise from embryonic rests of lymphatic tissue. The tumor may be asymptomatic. If it is large enough, the patient may notice an abdominal growth or complain of intermittent pain. Excision is the treatment of choice. The authors report a case of a large lymphangioma of the mesentery of the jejunum which was removed, with the patient making an uncomplicated recovery.

Bantin, Omaha.

Perforated Appendix in Children. Irwin Schulz, Arch. Surg. **56**:117 (Jan.) 1948.

From 1929 through 1946 there was a total of 226 children, 12 years of age and under, with perforated appendix at the Milwaukee Children's Hospital. Twenty-six of these died. The mortality was higher among the extremely young. The analysis showed that the mortality rate increased with the duration of illness at the time of admission to the hospital.

There was a steady reduction in the mortality rate since 1946. This reduction was obtained in the group who were critically ill. Important factors in reduction were the use of Wangensteen decompression, proper fluid and electrolyte balance, multiple small transfusions of whole blood, nonoperative treatment of the group in whom perforation had obviously occurred and the use of antibiotic substances.

Kaiser, Rochester, N. Y.

Antethoracal Transplantation of the Stomach in the Treatment of Congenital Atresia of the Thoracic Esophagus. William Francis Rienhoff Jr., Bull. Johns Hopkins Hosp. **82**:496 (April) 1948.

In patients in whom the atresia of the esophagus is so extensive that an end to end anastomosis is impossible, the author suggests another procedure: the antethoracal subcutaneous implantation of the stomach, with anastomosis to the esophagus just below the clavicle. The surgical technic is described and 2 cases reported. The operation is in one stage, can be carried out rapidly without shock to the patient and avoids the hazards of intrathoracic procedures.

Lyttle, Los Angeles.

REDUCTION OF INTUSSUSCEPTION BY HYDROSTATIC PRESSURE: AN EXPERIMENTAL STUDY. MARK M. RAVITCH and ROBERT M. MCCUNE JR., Bull. Johns Hopkins Hosp. **82**:550 (May) 1948.

The authors review the experimental work on the production of intussusception and describe their method of producing intussusception in dogs and the results of attempts at reduction by hydrostatic pressure.

A Foley bag catheter is placed in the rectum and saline solution is permitted to enter from a height of 3 feet (91.4 cm.). Pressure is maintained for five minutes. Up to thirty-eight hours, reduction was usually achieved by this method on one to three trials. After thirty-eight hours, the intussusception was not reducible. The pathologic features are described.

LYTTLE, Los Angeles.

PYLORIC STENOSIS NOT A DISEASE OF "FIRST-BORN." G. D. DELPRAT and OTTO PFLUEGER, California Med. **68**:76 (Feb.) 1948.

There is no evidence to support the statement that pyloric stenosis is a "disease of the first-born." The disease seems to be sporadic in its occurrence. The authors have seen families of 4 children with 3 involved, and these 3 were not consecutive children. They saw identical twins both of whom were affected and identical twins of whom only 1 was affected. In another family the condition occurred in children of several generations.

PRYOR, Redwood City, Calif.

ACUTE APPENDICITIS IN CHILDHOOD: A SUMMARY OF PRESENT CONCEPTS. WILLIAM J. NORRIS and DONALD BRAYTON, California Med. **68**:162 (March) 1948.

Children under 14 years of age account for almost one fourth of the over-all incidence of acute appendicitis. Certain anatomic factors of the child's appendix and its relationship to the peritoneal cavity favor relatively early perforation and poor localization of the infection. Abdominal pain, vomiting and slight elevation in temperature should always be considered as due to acute appendicitis until proved otherwise.

Principles of treatment recommended are operation as soon as possible after the diagnosis is made and the patient is adequately prepared; laparotomy if there is a reasonable doubt regarding diagnosis; the use of the McBurney incision in most instances; removal of the appendix concurrently with drainage of appendical abscess, and drainage of the abdomen in most cases of acute perforated appendicitis.

Refinements of treatment and the addition of chemical and antibiotic therapeutic agents have materially decreased the fatality rate of acute appendicitis in children. The chief factors affecting the mortality at present are the age of the patient and the delay prior to operation.

Practically all the deaths due to this disease in children fall within the group of those with acute appendicitis and perforation between the ages of 1 and 4 years. Special effort should be made to expedite the diagnosis in the very young, thus reducing the preoperative delay and, consequently, the mortality.

FROM THE AUTHORS' SUMMARY.

HYPERTROPHIC PYLORIC STENOSIS: A FOLLOW-UP STUDY. R. M. BENDER and H. NECHELES, J. A. M. A. **135**:331 (Oct. 11) 1947.

A follow-up study was conducted on 17 patients who had had the Ramstedt operation for pyloric stenosis in their infancy. Thirteen of the patients were men and 4 women. The families of most of the patients were also studied.

None of the patients had any symptoms relative to their operation. The incidence of peptic ulcer, below normal weight and highstrung and unstable personalities was high. In the families of the patients there was a large incidence of ulcer syndromes, spastic and mucous colitis and migraine.

It is suggested that hypertrophic pyloric stenosis is due to autonomic imbalance plus local irritation during embryonic life. BAIRD, Wauwatosa, Wis.

MECHANISM AND SIGNIFICANCE OF THE THYMOL TURBIDITY TEST FOR LIVER DISEASE. HENRY G. KUNKEL and CHARLES L. HOAGLAND, J. Clin. Investigation **26**:1060 (Nov.) 1947.

Serums from a group of 200 patients with infectious hepatitis and 65 patients with other hepatic diseases were used in studying the thymol turbidity reaction of Maclagan. Analysis of thymol precipitate showed that the turbidity produced by the action of thymol on lipemic serums of patients without hepatic disease was due to an increase in the particle size of protein-free lipid suspension, while turbidity produced by the reagent in clear serum from patients with hepatitis was due to formation of a protein-lipid-thymol complex. Four serums of varying lipid concentrations were added to positively reacting serum with a high gamma globulin level; the turbidity of resultant combination was proportional to amount of lipid in the added serum. No turbidity was obtained by adding the lipemic serums to normal serums. Correction for the turbidity due to lipid in this reaction was obtained by use of a photometric blank of serum and thymol reagent with such a high ionic buffer concentration that precipitation of globulin is prevented. Immunologic studies were done by obtaining an antibody to the protein in rabbit serum. However, the antiserum reacted with normal serum as well as with serum from patients with hepatitis.

Electrophoretic studies showed that the precipitate was in the gamma globulin fraction, but with rapid motility. A small definite beta globulin peak was also seen. Examination of serum from patients with hepatitis after removal of thymol protein showed that the largest part of precipitated protein came from the gamma globulin fraction and a small portion from the beta fraction.

In patients with acute infectious hepatitis, values for thymol turbidity were found to parallel alterations in serum lipids initially and alterations in gamma globulin during late convalescence. BRODSKY, Cincinnati.

THE INFLUENCE OF PTEROYLGLUTAMIC ACID (A MEMBER OF THE VITAMIN M GROUP) ON GASTROINTESTINAL DEFECTS IN SPRUE: A STUDY OF INTERRELATIONSHIPS OF DIETARY ESSENTIALS. WILLIAM J. DARBY, EDGAR JONES, HENRY F. WARDEN and MARGARET M. KASER, J. Nutrition **34**:645 (Dec.) 1947.

Darby and his associates present in this paper additional data which indicate that pteroylglutamic (folic) acid exerts a favorable influence on the gastrointestinal tract in sprue. The subjects were 6 adult patients with sprue who were observed in the Vanderbilt University Hospital, Nashville, Tenn. The sole specific therapeutic agent administered was synthetic pteroylglutamic acid in doses of either 5 mg. per day orally or 15 mg. per day intramuscularly, except in 1 case in which this was preceded by ten days' therapy with pteroyltriglutamate. During therapy 1 patient received a meat-free diet; the remainder were maintained on a regular ward diet devoid of organ meats. Observations on 6 patients with sprue during 7 remissions following therapy with pteroylglutamic acid are summarized. These findings are compatible with an interpretation that pteroylglutamic acid exerts a

favorable influence on the primary gastrointestinal disorder in sprue and thereby permits the correction of many secondary deficiencies which occur. Chronic sprue responds less completely to pteroylglutamic acid. Sprue and pernicious anemia differ in that gastrointestinal defects are more pronounced in sprue.

FREDEEN, Kansas City, Mo.

HYPERTROPHIC PYLORIC STENOSIS. H. O. BAKER, H. H. HARDY JR. and H. A. WHITE, New Orleans M. & S. J. **100**:307 (Jan.) 1948.

A brief discussion of pyloric stenosis is presented, with a description of the operative technic. Eighteen patients were operated on by the standard Fredet-Ramstedt technic, with no mortality.

McGUIGAN, Evanston, Ill.

MARKED HYPOKALEMIA IN PROLONGED DIARRHEA: POSSIBLE EFFECT ON HEART. ALICE H. GAMBLE, HILDA F. WIESE and ARILD E. HANSEN, Pediatrics **1**:58 (Jan.) 1948.

An extremely low concentration of potassium was found in the serum of an infant with diarrhea of one month's duration. In spite of the daily administration of potassium chloride, the hypokalemia (1 to 1.3 milliequivalents per liter) persisted for one week. The serum potassium returned to a normal level after the administration of a total of 108 millimols of potassium or about one fifth of the estimated content of the body. During the hypokalemic state, definite cardiac changes developed, as evidenced by pronounced tachycardia, apical systolic murmur and electrocardiographic changes. These abnormalities improved, and the heart was normal five days after the serum potassium returned to a normal level. Recovery was complete, and examination of the infant four months after her dismissal from the hospital showed her to be normal in all respects.

FROM THE AUTHORS' SUMMARY.

THE ETIOLOGY OF EKIRI, A HIGHLY FATAL DISEASE OF JAPANESE CHILDREN. KATHARINE DODD, G. JOHN BUDDINGH and SAMUEL RAPOPORT, Pediatrics **3**:9 (Jan.) 1949.

In the summer 1947, a team from the United States, consisting of a clinician, a bacteriologist and pathologist and a biochemist, went to Tokyo, Japan, under the auspices of the Japanese Institute of Health and Public Health and Welfare Section of the Supreme Command of the Allied Powers to study the disease ekiri. They observed that patients with ekiri had definite signs and symptoms of tetany, as well as of dysentery. The symptoms were hyperventilation, lethargy or delirium, tonic muscle spasms, disturbances in the autonomic nervous system and severe clonic or tonic convulsions. Less severe signs and symptoms of tetany were seen when the diagnosis of bacillary dysentery was made. Cultures from the stools of 106 patients yielded dysentery bacilli in almost every case. Postmortem examination revealed inflammation of the colon compatible with dysentery in most patients.

The chemical disturbance was characterized by low serum levels of calcium, a decrease in carbon dioxide content and tension of the blood and high levels of nonprotein nitrogen. Low calcium levels appeared compatible with clinical signs of tetany. Decreased carbon dioxide tension and presence of normal $p_H$ values evidenced the extreme degree of hyperventilation observed clinically. Elevation of the nonprotein nitrogen appeared explicable by the great losses of water caused by high fever and hyperventilation, added to losses of body fluid through vomiting and diarrhea.

Japanese infants are breast fed for the most part and are weaned at 1 to 2 years of age. The diet of the children, similar to that of the adults, is low in calcium; children 2 to 6 years of age get about 0.15 Gm. per day. Rickets is uncommon.

An orienting study was carried out on 29 Japanese children 2 to 6 years old. Mild signs of tetany were noted in a considerable proportion of them; 5 showed serum calcium levels below 9 mg. per hundred cubic centimeters of blood. Phosphorus levels tended to be higher than those of American control groups. Serum alkaline phosphatase was considerably elevated, sometimes in excess of 10 Bodansky units. Roentgenograms showed no rickets but suggested decreased mineralization. These data support the assumption of calcium deficiency in the diet. The authors concluded that ekiri is mostly bacillary dysentery complicated by tetany. Its treatment with calcium chloride, sulfonamides and large amounts of fluids parenterally produced some improvement in the mortality rate. Increasing the calcium intake of Japanese children and introducing public health measures to cut down dysentery should largely prevent its occurrence.

FROM THE AUTHORS' SUMMARY.

CHRONIC INTUSSUSCEPTION. HENRY A. REISMAN and ARTHUR P. WOLK, Pediatrics **4**:183 (Aug.) 1949.

Two cases of chronic intussusception are presented. The intussusceptum was formed in one child (case 1) by an inverted appendix and in the other (case 2) by an invaginated Meckel diverticulum. Both these children, boys, aged 5 years and 26 months, respectively, were admitted to the hospital with histories of intermittent abdominal pain of several weeks' duration. The older boy showed both gross and occult blood in the stools at intervals but the stools for the most part were soft and occurred once daily, although there was occasional mild diarrhea or constipation. There was no change in the bowel habits in the younger child, although occult blood was found in the stool. Vomiting, completely absent in the younger boy, was a minor sign in the older. Rectal examination showed no abnormality in either child. In both patients the diagnosis of partial intestinal obstruction was confirmed only after roentgenologic studies with an opaque substance had been completed.

Although both children displayed anorexia and loss of weight, the one outstanding clinical symptom was intermittent colicky abdominal pain. It is therefore pertinent that chronic intussusception be considered in the differential diagnosis of all cases of persistent colicky abdominal pain, even though unaccompanied with evidence of obstruction.

FROM THE AUTHORS' SUMMARY.

NEW CONCEPTS OF CONGENITAL MEGACOLON. ORVAR SWENSON, EDWARD B. D. NEUHAUSER and LAWRENCE K. PICKETT, Pediatrics **4**:201 (Aug.) 1949.

Congenital megacolon, or Hirschsprung's disease, is due to a functionally abnormal segment of bowel in the sigmoid or rectosigmoid. This can be demonstrated effectively by appropriate roentgenologic studies with barium sulfate as a contrast medium. The bowel above this abnormally functioning segment shows changes commonly found above an area of obstruction, dilatation and hypertrophy.

Removal of the functionally abnormal segment of bowel (rectum or rectosigmoid) relieves the patients' symptoms. A new operative technic is utilized in performing this resection. The fact is stressed that these children will have to be followed for several years before any claims of a permanent cure can be made.

FROM THE AUTHORS' SUMMARY.

STUDIES IN PANCREATIC FIBROSIS: A SIMPLE DIAGNOSTIC GELATIN FILM TEST FOR STOOL TRYPSIN. HARRY SHWACHMAN, PAUL R. PATTERSON and JOSÉ LAGUNA, Pediatrics **4**:222 (Aug.) 1949.

A simple test is described for the estimation of the proteolytic activity of stools with the use of unexposed, unfixed strips of roentgenogram film. An emulsion of the stool is placed on the film and after incubation the film is washed in a stream of cold water. The presence of tryptic activity is indicated by a clearing of the gelatin, whereas no change signifies absence of activity. This test was performed on specimens from 500 normal and sick patients, as well as on those from 50 patients ill with pancreatic fibrosis. The incidence of negative reactions increases with age in normal persons.

A total of 220 tests was performed on 50 patients with pancreatic fibrosis; all but 11 specimens (from 7 patients) showed no tryptic activity. This test is proposed as a screening measure for diagnostic study in cases of suspected pancreatic fibrosis, provided three separate stool specimens are examined. The effectiveness of pancreatin given orally has also been followed by this test.

FROM THE AUTHORS' SUMMARY.

## Nervous Diseases

STURGE-WEBER SYNDROME. ARCHIBALD D. MCCOY and HAROLD C. VORIS, Arch. Neurol. & Psychiat. **59**:504 (April) 1948.

A detailed discussion is presented of the syndrome of associated facial nevi, intracranial lesions and ocular changes, including causation pathologic aspects, symptomatology and treatment. The case of a child first seen at the age of 13 years is presented, with follow-up notes made over a period of seven years.

MCGUIGAN, Evanston, Ill.

CARBONIC ANHYDRASE IN THE CENTRAL NERVOUS SYSTEM OF THE DEVELOPING FETUS. W. ASHBY and E. BUTLER, J. Biol Chem. **175**:425 (Aug.) 1948.

The erythrocytes and various portions of the brain of 6 infants and 3 adults were analyzed for their content of the enzyme carbonic anhydrase. The red blood cells of the premature infants contained small amounts of the enzyme (less than 30 units per cubic centimeter), while those of the full term infant and the adult revealed considerably larger amounts (145 and 600 units, respectively). The adult brain contained carbonic anhydrase in all its sectors, the pons and forebrain showing the highest values. In contrast, no carbonic anhydrase was in the premature cerebrum and small amounts were in the medulla, pons, cerebellum and midbrain, while the spinal cord content equaled that of the adult. With lengthening gestation there was a progressive change toward the adult pattern.

The report also presents data on the brains of fetal calves.

FORBES, St. Louis.

CEREBRAL ABSCESS: A COMPLICATION OF CONGENITAL CARDIAC DISEASE (FALLOT'S TETRALOGY). A. HAND, J. Pediat. **31**:662 (Dec.) 1947.

A fatal case of cerebral abscess in a 4½ year old boy complicating the tetralogy of Fallot is reported with observations at autopsy. In addition, a second case, in which surgical drainage was employed, but with death later because of a sec-

ond abscess, is reported with brief postmortem observations. A review of the literature and the mention of 2 additional unreported cases yield a total of 36 cases.

The author states that the complication of cerebral abscess is more frequent than usually suspected and should receive increased attention in textbooks and from physicians and other caretakers of patients with congenital cardiac disease.

C. G. Grulee, Jr., Galveston, Texas.

Occult Meningocele of the Sacrum. V. W. Archer, George Cooper and C. V. Cimmino, Radiology **51**:691 (Nov.) 1948.

The authors report 3 cases and emphasize that occult meningocele is a distinct entity, although much of the literature has included it under "spina bifida occulta." The difference is the presence of a dilated dural sac with or without herniation into the soft tissues. The usual striking symptom is lack of bladder control. Occasionally, there are toe drops and saddle anesthesia, pain in the posterior part of the leg or low back pain. Myelograms revealed iodized oil far below the usual caudal limit of the dural sac in 3 cases. In 1 a meningocele the size of a lemon was first discovered at operation. After a presumptive diagnosis of neurofibroma, the normal sacral landmarks were obliterated in one case and a defect in the vertebral arches of the sacrum appeared on the roentgenograms in another.

Anspach, Chicago.

Cerebellar Atrophy. J. D. Spillane, Proc. Roy. Soc. Med. **41**:861 (Dec.) 1948.

This case was reported of a girl 16 years of age. The onset, family history and results of physical examination are given in the report. An encephalographic study showed a little excess air over the cerebral cortex, with cerebellar atrophy, as judged by the increased size of the left ventricle, the excess of interfolial air and a general increase of air in the posterior cranial fossa.

Williamson, New Orleans.

The Small Blood Vessels of the Skin in Meningitis. P. Nicolai, Clin. pediat. **30**:89 (Feb.) 1948.

Microscopic observations were made on the capillaries of the skin in 23 children with meningitis. In those with meningococcic meningitis, there was a spastic narrowing of the vessels, that disappeared as the patient became well or was followed by dilatation in the fatal cases; there was an increased capillary fragility. In patients with tuberculous and influenzal meningitis, at first a spasm of the capillaries occurred, followed by dilatation as death approached; the capillary fragility was normal but sometimes it was increased in the terminal stages of the disease. In pneumococcic meningitis, capillary dilatation was present even from the beginning of the disease; the capillary fragility remained normal.

Higgins, Boston.

Infantile Toxoplasmic Encephalomyelitis. Paolo Tolentino and Antonio Bucalossi, Policlinico inf. **16**:245 (June) 1948.

The authors describe 2 cases of infantile toxoplasmosis. The first case was that of a female infant who became ill at the age of 6 months with frequent convulsions and physical and psychic impairment. There were ocular lesions (coloboma

of the iris, refractive defects and active bilateral chorioretinitis), internal and communicating hydrocephalus and spasticity of the lower extremities. The second case was that of a male infant who became ill at 3½ months of age with convulsions, fever and vomiting; there were in this case neurologic symptoms, internal and communicating hydrocephalus and deposits of calcium in the brain demonstrable on roentgenologic examination. No lesions of the fundus were present but an extensive depigmentation of the retinas was noted. The cerebrospinal fluid was found to be normal or subnormal in the 2 cases (it was examined a few months after the onset of the disease). Sabin's test for Toxoplasma neutralizing antibodies gave a positive reaction in the first case; in the second case the reaction was positive for the serum of both parents, but not for the patient's serum. The 2 cases are discussed from a diagnostic point of view, with reference to other diseases causing convulsions, ocular lesions and calcifications, and in relation to atypical forms of toxoplasmosis. The prognosis is serious. The treatment with sulfonamides and nonspecific vaccines resulted in no definite improvement in either case.

FROM THE AUTHORS' SUMMARY.

NEW TECHNIC FOR SPINAL AND VENTRICULAR DRAINAGE IN SYMPTOMATIC TREATMENT OF INTRACRANIAL HYPERTENSION. G. PASQUINUCCI and A. MILANI-COMPARETTI, Riv. clin. pediat. **47**:70 (Jan.) 1949.

A new technic is described for the symptomatic treatment of intracranial hypertension from hydrocephalus and for the local application of streptomycin in the arachnoidal spaces and in the ventricular cavities. The method is based on the use of a permanent catheter connected with an apparatus which regulates the flow of the spinal fluid and the intracranial pressure.

FROM THE AUTHORS' SUMMARY.

MENINGITIS CAUSED BY LISTERELLA MONOCYTOGENES. G. W. VAN DRIEST and J. SLOOFF, Maandschr. v. kindergeneesk. **16**:101-110 (April) 1948.

In November 1947, a 10 day old infant was admitted to the children's hospital at Groningen, Netherlands. The temperature was elevated and, besides an inflammation of the umbilicus, the child had meningitis. The cell content of the spinal fluid was increased, half the cells being lymphocytes. In the direct smear no bacteria were seen. From the spinal fluid and from the blood Listerella monocytogenes was cultured. This bacterium is a gram-positive, aerobic rod which is motile at 20 C. (68 F.). The diagnosis was confirmed by the results of the agglutination test with specific antiserum.

In 1926, this micro-organism was isolated for the first time by Murray, Webb and Swarm and by Pirie from sick rabbits and mice with fever, necrotic foci in the liver and mononucleosis. In 1932, the bacterium was cultured by Kapsenberg from the spinal fluid of a patient with meningitis. Since then, several cases of meningitis, as well as some cases of sepsis and pneumonia, caused by Listerella monocytogenes, have been reported.

Following inoculation of the eye of a rabbit with a drop of the culture, conjunctivitis and keratitis developed, the keratitis showing a typical picture; inoculation into the rabbit's eye can be used to differentiate L. monocytogenes from Erysipelothrix. One case was observed in which the meningitis was preceded by a purulent conjunctivitis. The possibility has to be considered that some cases of conjunctivitis in man may be caused by Listerella.

L. monocytogenes has only a slight sensitivity to penicillin and sulfadiazine. Two-tenths unit of penicillin per cubic centimeter inhibits growth in vitro. Streptomycin in a concentration of 1 unit per cubic centimeter is effective.

The aforementioned infant recovered after treatment with penicillin and large doses of sulfadiazine. The treatment with streptomycin combined with one of the sulfonamide drugs in large dosage is recommended.

Another case of meningitis caused by L. monocytogenes is reported. The patient was a 10 day old infant, who also recovered after treatment with penicillin and sulfadiazine. The patient's mother died from meningitis four days before the child was admitted to the hospital. In the direct smear from the spinal fluid of the mother gram-positive rods were seen. Attempts at isolation of the bacteria failed.

VAN CREVELD, Amsterdam, Netherlands.

BABINSKI PHENOMENON AND THE SO-CALLED BALL BABINSKI REFLEX. ULRICH FLECK, Med. Klin. **44**:372 (March 25) 1949.

The Babinski reflex is discussed, and attention is called to the fact that it can be elicited sometimes only when a stroke of medium strength is applied over the balls of the toes from the small toes to the large ones.

AMBERG, Rochester, Minn.

ORIGIN OF TENTORIUM TEARS. HANS JOACHIM SCHWENGLER, Med. Klin. **44**:471 (April 15) 1949.

The author concludes that the primary cause of a tentorium tear with intracranial bleeding is a deficient constitution. All other factors are secondary.

AMBERG, Rochester, Minn.

## Diseases of the Genitourinary Tract

OCULAR MANIFESTATIONS IN CONGENITAL HEMATOPORPHYRINURIA. P. CARRERAS DURAN, Arch. Soc. oftal. hispano-am. **7**:459 (May) 1947.

The author had the opportunity to observe the ocular manifestations of the rare condition of congenital hematoporphyrinuria in a man, aged 49. The patient presented the characteristic dermatologic signs of the disease in the face. Owing to the extension of these lesions, cicatricial ectropion was present in both lower lids. There were chronic bilateral conjunctivitis and extensive adherent scarring of the conjunctiva in the nasal aspect of the interpalpebral fissure, simulating bilateral pseudopterygium. In both eyes was a circular, cleancut area of absence of scleral tissue, about 2 mm. in diameter, on the external aspect of the sclera in the horizontal meridian and 3 mm. from the limbus. The area was covered by the conjunctiva, and the uveal pigment could be seen through it. Two similar lesions, although not so well developed, were found in the upper part of the left globe. There were subepithelial nebulas in the cornea in the right eye, with some vascularization of the inferior part.

Visual acuity with correction was 6/10 in the right eye and 2/10 in the left eye. The visual fields and color vision were normal.

The author states that the lesions of the sclera are the most important. He is of the opinion that they are analogous to the lesions described by van der Hoeve as scleromalacia perforans, 9 cases of which have been reported in the literature.

The article is illustrated with colored plates.

CARRASQUILLO [ARCH. OPHTH.].

Pubertas Precox. Philip Sandblom, Nord. med. (Hygiea) **36**:2200 (Oct. 31) 1947.

A boy 6 years of age was first seen one year after he had begun to display increasing signs and symptoms of precocious puberty. At the examination he was noted to be tall, with adult-sized external genitals, one-sided enlargement of the testes without clinical signs of a tumor, normal sella turcica and normal thyroid. Urography gave no indication of abnormality. Excretion of 17-ketosteroids was 23 to 26 mg. daily, increasing to 61 mg. Excretion of chorionic gonadotropin was normal. Intelligence corresponded to his actual age. The skeletal development corresponded to that of 6 to 7 years of age. An exploratory operation on the adrenal glands showed suspected enlargement of the left gland, which was extirpated without improvement of the symptoms. Then the enlarged testis was extirpated and in this was found an interstitial cell tumor (Leydig's tumor). After the operation, the excretion of 17-ketosteroids decreased to 13 mg., the physical development was arrested and other signs of precocious puberty were less prominent.

Wallgren, Stockholm, Sweden.

Hormonal Treatment in Deficient Descent of the Testes. Alfred Sundal, Tidsskr. norske lægefor. **67**:43 (Feb. 1) 1947.

The treatment of retention of the testes in 14 boys (bilateral in 4 cases) is reported on. Two hundred mouse units of gonadotropic hormone was given in 10 injections, with satisfactory descent of thirteen testes, of which all but one were palpable in the inguinal area before treatment. Of six cryptorchitic testes only one responded to the hormonal treatment. This treatment should begin at 8 years of age and if unsuccessful should immediately be followed by surgical treatment. In 4 boys operation was performed, with good results in 2.

Wallgren, Stockholm, Sweden.

## Diseases of the Ductless Glands: Endocrinology

Effect of Reciprocal Steroid Treatment on the Electrophoretic Patterns of Fowl Sera. Dan H. Moore, Endocrinology **42**:38 (Jan.) 1948.

Sex differences in the electrophoretic pattern of chicken serum appeared at the beginning of sexual maturity. Hen and cock serum patterns were reversed by contrasex hormones.

Jacobsen, Buffalo.

Anatomical Comparison Between the Adrenal Glands of Wild Norway, Wild Alexandrine and Domestic Norway Rats. Philip V. Rogers and Curt P. Richter, Endocrinology **42**:46 (Jan.) 1948.

The observations reported demonstrate that one of the striking changes undergone by the Norway rat during its many generations of laboratory life is a great decrease in the size of the adrenal glands in animals of both sexes.

Jacobsen, Buffalo.

The Chemical Histology and Cytology of the Pineal Body and Neurohypophysis. George B. Wislocki and Edward W. Dempsey, Endocrinology **42**:56 (Jan.) 1948.

This paper gives an account of cytologic and histochemical features of the pineal body and neurohypophysis of the rhesus monkey. It concerns observations

on the presence and distribution of nucleoproteins, lipids, glycogen, collagen, nerve fibers and alkaline phosphatase explored by a variety of methods. It contains brief observations also in regard to autofluorescence and birefringence in these areas.

JACOBSEN, Buffalo.

THE EFFECT OF DIETARY PROTEIN CONTENT UPON THE NITROGEN RETENTION AND WEIGHT GAIN PRODUCED BY THE HYPOPHYSEAL GROWTH HORMONE. GILBERT S. GORDON, LESLIE L. BENNETT, CHOH HAO LI and HERBERT M. EVANS, Endocrinology **42**:153 (March) 1948.

The fact that hypophysial extracts rich in growth hormone produce nitrogen retention has been shown repeatedly. In these experiments the authors used a standard dose of the growth hormone and compared the gain in weight and the nitrogen retention in rats fed constant amounts of isocaloric diets with varying protein content.

The amount of nitrogen retained and the increment of weight gained under the influence of a five day period of injection of the hypophysial growth hormone both varied concordantly with the dietary protein content. The 24 per cent casein diet was optimal for the dose of growth hormone employed. The amount of nitrogen retained, calculated as protein plus protein-bound water, corresponded closely to the observed gain in weight.

JACOBSEN, Buffalo.

AN ATTEMPT TO EXPLAIN THE ANOMALOUS ACTION OF LUGOL'S SOLUTION IN EXOPHTHALMIC GOITER. J. F. MCCLENDON, W. C. FOSTER and J. W. CAVETT, Endocrinology **42**:168 (March) 1948.

A goiter is considered to be a thyroid gland enlarged by compensatory hypertrophy and, therefore, capable of producing more thyroglobulin than the normal thyroid. Hocher, of Berne, Switzerland, would not allow iodine to be used on his patients with goiter for fear of making them all hyperthyroid, but Plummer, of the Mayo Clinic, gave his patients strong iodine (Lugol's) solution U. S. P. and demonstrated its anomalous action in lowering the basal metabolic rate in exophthalmic goiter.

To investigate this phenomenon, the following experiments were carried out: The thyroid and pituitary glands of 216 12 week old chickens were weighed and analyzed for protein-bound iodine. One third had been given 0.2 per cent thiouracil in the feed; one third had 4 cc. of strong iodine solution added per gallon (3.8 L.) of drinking water, and one third were used as controls.

Thiouracil definitely increased both wet and dry weight of the thyroid glands and reduced the protein-bound iodine to 10 per cent of its normal value. The protein-bound iodine of the pituitary glands was reduced to 85 per cent of its normal value.

Strong iodine solution increased the protein-bound iodine of the thyroid 133 per cent and of the pituitary 48 per cent. It seems probable that local action of this protein-bound iodine in the pituitary might inhibit the release of thyrotropin and explain the anomalous action of strong iodine solution in exophthalmic goiter.

JACOBSEN, Buffalo.

THE PATHOLOGY OF THE ADRENAL GLAND IN ADDISON'S DISEASE WITH SPECIAL REFERENCE TO ADRENOCORTICAL CONTRACTION. NATHAN B. FRIEDMAN, Endocrinology **42**:181 (March) 1948.

"Cytotoxic" necrosis, atrophy or contraction of the adrenal cortex associated with functional insufficiency have been recognized as a clinicopathologic entity for

many years. It is also well known that the incidence of adrenocortical contraction as a cause of Addison's disease now equals or exceeds that of tuberculosis of the adrenal gland.

Pathologic material from 15 patients who exhibited adrenocortical contraction at autopsy was studied. During the same period specimens from only 10 patients with Addison's disease caused by tuberculosis were collected.

The clinical syndrome was in many instances so atypical and confusing that the diagnosis of adrenal insufficiency was not entertained, particularly when the disease ran a short, fulminating course. Acute gastroenteritis, poisoning, ruptured peptic ulcer, coronary occlusion, psychosis, intracranial hemorrhage and myasthenia gravis were all simulated. The danger of temporizing with the medical emergency of adrenal insufficiency was underlined by the repeated occurrence of sudden collapse and death. The morphologic picture of full-blown adrenocortical contraction ranged from that of pure destructive atrophy, or collapse of the cortex, to that in which the regeneration of cortical cells and nodules in atypical patterns overshadowed and masked the underlying atrophy.

JACOBSEN, Buffalo.

THE INFLUENCE OF HYPOPHYSECTOMY, THYROIDECTOMY, AND OF BOTH HYPOPHYSECTOMY AND THYROIDECTOMY UPON THE FAT CONTENT OF THE LIVER OF THE DOG. C. ENTENMAN, I. L. CHAIKOFF and F. L. REICHERT, Endocrinology **42**:210 (March) 1948.

The control exercised by pituitary and thyroid glands on lipid metabolism and blood lipids is well known. It is shown in the present investigation that the control of these glands over lipid metabolism is not limited to blood. In dogs deprived of the thyroid alone fatty livers may be present, but in those deprived of both glands fatty livers are an invariable occurrence. Thus, the lipid changes in the livers in these animals parallel those observed in the blood.

JACOBSEN, Buffalo.

CHOLINE PREVENTS FATTY CHANGE AND CIRRHOSIS IN THE LIVERS OF DOGS SUBJECTED TO HYPOPHYSECTOMY AND THYROIDECTOMY. C. ENTENMAN, I. L. CHAIKOFF, T. GILLMAN and F. L. REICHERT, Endocrinology **42**:215 (March) 1948.

It has been demonstrated that fatty and cirrhotic livers occur in dogs which have been hypophysectomized and thyroidectomized. It is shown in this paper that the addition of free choline to the diet of these doubly operated on dogs not only completely prevents the accumulation of fat in their livers but results as well in an almost complete suppression of the hepatic fibrosis. This new observation suggests that the removal of both glands has in some way interfered with the availability or utilization of the lipotropic factors contained in the diet or has increased the animal's requirements for these substances. Thus, this study brings to light a new aspect of the action of ingested lipotropic foodstuffs, namely, their dependence on endocrine factors.

JACOBSEN, Buffalo.

THE USE OF THE MALE NORTH AMERICAN FROG (RANA PIPIENS) IN THE DIAGNOSIS OF PREGNANCY. STANLEY L. ROBBINS and FREDERIC PARKER JR., Endocrinology **42**:237 (April) 1948.

A new test for pregnancy, utilizing the release of spermatozoa by the male Rana pipiens on stimulation with mammalian chorionic gonadotropin is described. The ease with which a diagnosis of pregnancy can be established with this test makes

possible the adoption of this technic in any laboratory, however small. The rapidity that it affords makes of the test an emergency procedure of possible benefit in difficult diagnostic problems.

JACOBSEN, Buffalo.

CONDITIONS ASSOCIATED WITH THE SECRETION OF THE ADRENAL CORTEX. C. N. H. LONG, Federation Proc. **6**:461 (Jan.) 1947.

Long reviews some of the recent work, including his own extensive contributions, on the function of the adrenal cortex. From available information it is apparent that all circumstances enhancing cortical secretions do so by first activating the anterior lobe of the pituitary, which then releases the adrenocorticotropic hormone. The observation that the adrenal cortex is richer in cholesterol (4 Gm. per hundred cubic centimeters) and ascorbic acid (400 mg. per hundred cubic centimeters) than any other tissue, with the exception of the corpus luteum, led to a study of the concentration of these two substances in the gland as a means of quantitating adrenal response. The cholesterol and ascorbic acid concentrations of the adrenal cortex regularly fall under various conditions of stress, such as hemorrhage, cold, burns, injections of bacteria, anoxemia and injections of epinephrine, and the results were strongly indicative that epinephrine is the common denominator. Increased excretion of "cortins" was noted in these experiments and suggested that perhaps adrenal cholesterol is the precursor of at least some of the cortical hormones. Hypophysectomy abolished these effects. The administration of 1 to 4 mg. of adrenocorticotropic hormone to normal rats produced within three to nine hours a 50 per cent drop in adrenal cholesterol, a 60 per cent drop in adrenal ascorbic acid, a 75 per cent drop in circulating lymphocytes and an increase of 400 per cent in hepatic glycogen. The implications of this type of approach to adrenal physiology and the role of the adrenal cortex in health and disease are apparent.

FORBES, St. Louis.

THE EXCRETION OF 17-KETOSTEROIDS AND GONADOTROPIN IN CHILDREN: NORMAL AND ABNORMAL CASES. A. M. HAIN, Arch. Dis. Childhood **22**:156 (Sept.) 1947.

A knowledge of the excretion of 17-ketosteroids and gonadotropin is helpful to the clinician in dealing with developmental anomalies in children. Gonadotropin can be detected in normal girls before the seventh year and in normal boys before the ninth year. In a study of children of both sexes in whom development was precocious, gonadatropin was excreted in amounts considerably above the average for the chronologic age. Precocious menstruation without a pathologic background is probably associated with abnormal tissue response, as well as premature secretion from the pituitary.

KELLY, Milwaukee.

THE INTERRENAL SYNDROME IN CHILDHOOD. E. C. ALLIBONE, H. S. BAAR and W. H. P. CANT, Arch. Dis. Childhood **22**:210 (Dec.) 1947.

From a review of the case material of the Children's Hospital, Birmingham, England, during the last ten years, 10 patients with adrenal hyperplasia of the newborn with symptoms of adrenocortical hypofunction are described and the symptomatology and the diagnosis discussed. The estimation of the urinary chloride as a diagnostic aid is emphasized. The differences in the clinical picture between the adrenogenital syndromes in the newborn and in older children are pointed out.

Five further children with adrenal hyperplasia in the newborn are described, 2 with hemolytic disease of the newborn, 2 with exomphalos and 1 a stillborn child with glycogenosis.

The adrenogenital syndrome in older children is represented by 3 patients, the condition in all due to hyperplasia. One boy presented the typical picture of macrogenitosomia precox. The 2 girls were pseudohermaphrodites. Two girls with adrenocortical obesity, or Cushing's syndrome, due to adrenocortical carcinoma are described. The liability of such children to sudden death is stressed.

An attempt is made to correlate the two syndromes with histologic changes in the adrenal cortex. Although the proportion of transient to permanent cortex was variable in children with adrenal hyperplasia of the newborn, the transient cortex predominated in the adrenogenital syndrome in older children but was completely absent in the atrophic adrenal gland contralateral to the carcinoma in those with Cushing's syndrome.

FROM THE AUTHORS' SUMMARY.

FETAL CELL ADENOMATA OF THE HYPOPHYSIS CEREBRI. M. L. BAYOUMI, Edinburgh M. J. **55**:750 (Dec.) 1948.

Of 105 chromophobe adenomas removed surgically, 35 contained fetal cells either entirely or in part. The majority of fetal cell adenomas or tumors containing fetal cells along with chief or transitional cells have a duration of less than five years. Fifty-five per cent of chromophobe adenomas with a duration of less than one year are of the fetal cell type.

Twenty-four subclinical chromophobe adenomas were discovered in another group of 200 autopsies. Of these, 9 adenomas contained fetal cells.

MACDONALD, Pittsburgh.

SUPRA-HYOID CYSTS CAUSING DYSPNOEA IN INFANTS. S. PEARLMAN, Clin. Rep. Adelaide Children's Hosp. **1**:28 (May) 1947.

Pearlman reports on 3 infants admitted to the hospital with diagnoses of congenital laryngeal stridor or enlarged thymus, who were discovered to have suprahyoid cysts. He comments on the paucity of references in the literature and expresses his opinion that this condition should always be considered in the diagnosis of congenital stridor.

MCGUIGAN, Evanston, Ill.

CUSHING'S SYNDROME IN A CHILD EIGHT YEARS OF AGE. H. PEITSARA, Ann. med. int. Fenniae **36**:332, 1947.

A typical case of Cushing's disease of the pituitary in a girl of 8 years is reported. The symptoms had begun six months previously with obesity of face and body, hirsutism, plethoric cyanosis, severe osteoporosis, muscular flabbiness, headache, vertigo, epileptiform fits, mental depression, hypertonia and diabetes insipidus. She displayed hyperglycemia, high dextrose tolerance, a tendency to increased nonprotein nitrogen and glycosuria. The sella turcica was normal. Considerable improvement was noted after roentgen treatment. When last heard of six months later, she was still free from symptoms.

WALLGREN, Stockholm, Sweden.

MALIGNANT RETROPERITONEAL NEUROBLASTOMA IN A CHILD. FRANK BERGAN, Nord. med. (Norsk mag. f. lægevidensk. **36**:2499 (Dec. 12) 1947.

A girl 6 years of age was first seen three months after she had begun showing symptoms and signs of abdominal tumor. She had protrusion of the eyeballs, chemosis of the conjunctivas and anemia. Hemoglobin measured 48 per cent.

There were 3,520,000 red blood cells and 5,500 white blood cells with 51 per cent lymphocytes and a shift to the left of the leukocytes. A biopsy specimen of the bone marrow showed a paramyeloblastic picture (tumor cells?). The clinical diagnosis was acute paramyeloblastic leukemia. The autopsy revealed the Hutchinson type of neuroblastoma originating in the left adrenal gland.

WALLGREN, Stockholm, Sweden.

## Diseases of the Muscles, Bones, Joints and Lymph Nodes

CASE OF RIBBING'S DISEASE OF THE MICROEPIPHYSIS TYPE. G. FANCONI, Helvet. paediat. acta **2**:33 (Jan.) 1947.

A description of 1 case of dysostosis enchondralis epiphysaria (Ribbing's disease) of the microepiphysis type is given. FROM THE AUTHOR'S SUMMARY.

SYNDROME OF CONGENITAL ARTHROMYODYSPLASIA: CONTRIBUTION TO THE STUDY OF ARTHROGRYPOSIS MULTIPLEX CONGENITA. ETTORE ROSSI, Helvet. paediat. acta **2**:82 (Jan.) 1947.

Rossi reports 8 cases of arthrogryposis multiplex congenita (syndrome of congenital arthromyodysplasia) recently observed in the Children's Hospital, Zurich. The disease is degenerative and characterized essentially by decreased mobility of joints, which may lead to ankylosis. This disease usually attacks the four extremities and is always accompanied with serious changes in muscle, such as hypoplasia and aplasia, and other deformities, especially of the limbs.

Frequently, subcutaneous dysplasia and changes in the kneecap and in the lower jaw have been noted. In 1 patient observed roentgenologically before birth, histologic examination showed no inflammatory change of affected joints. Etiopathogenic theories which assume a mechanical cause must be rejected. The condition is probably hereditary, in analogy to other multiple congenital deformities.

FROM THE AUTHOR'S SUMMARY.

INHERITANCE OF THE BONNVIE-ULLRICH SYNDROME. ETTORE ROSSI and ERNST HOWALD, Helvet. paediat. acta **2**:98 (Jan.) 1947.

Rossi and Howald report on two families in which the Bonnevie-Ullrich syndrome was hereditary. This is probably a facultatively dominant hereditary disease.

FROM THE AUTHORS' SUMMARY.

ACHONDROPLASTIC KYPHOSIS IN A CHILD WITH MYXEDEMA. L. BARTA and K. GEFFERTH, Paediat. danub. **3**:65 (Feb.) 1948.

A girl 7 years of age had kyphosis and myxedema. Following massive medication with thyroxin, thyreotoxic symptoms developed which ceased spontaneously after six weeks. The galactose tolerance curve was flat and characteristic of myxedema even during the thyreotoxicosis, and no galactose could be found in the blood. This meant that in spite of the thyreotoxicosis the liver preserved its ability to store and assimilate galactose, a function which always remains intact in hypothyroidism. Following administration of epinephrine, the dextrose tolerance curve was pathologically high during the toxic state but became normal after the symptoms had ceased.

The patient had two diseases at the same time, hypothyroidism and chondrodystrophy, both of which lead to endochondral defects. The skeletal deformity was due to chondrodystrophy. The lack of effectiveness of treatment with thyroid extracts offered further proof of this supposition.

FROM THE AUTHORS' SUMMARY.

## Cutaneous Diseases; Allergy

THE PROBLEMS OF EPIDEMIC RINGWORM OF THE SCALP. SAMUEL J. ZAKON and AARON L. GOLDBERG, Illinois M. J. **92**:232 (Oct.) 1947.

This review of the causation, modes of transmission, clinical description, diagnosis, prophylaxis and treatment of epidemic ringworm of the scalp is too detailed for adequate abstracting.

BARBOUR, Peoria, Ill.

THERAPY OF ALLERGY: FACTS AND FANCIES. SAMUEL M. FEINBERG, Illinois M. J. **92**:234 (Oct.) 1947.

The therapy of allergic manifestations consists of the systematic and appropriate employment of methods of avoiding or eliminating the specific antigen, specific desensitization to gain tolerance, the judicious use of palliative remedies, including the new histamine antagonists, and other means in special instances. These legitimate therapeutic tools are often misunderstood and misapplied, frequently because of overenthusiasm and sometimes because of lack of sufficient interest. There is more immediate potential benefit to the allergic population from the proper application of facts about allergy already known than is likely to result from new discoveries in the near future.

FROM THE AUTHOR'S SUMMARY.

NEURO-ALLERGY IN CHILDHOOD. T. WOOD CLARKE, New York State J. Med. **48**:393 (Feb. 15) 1948.

Pediatricians are now stressing the importance of allergy more and more, but they are not yet fully conversant with its implications in the meninges and the brain. Three characteristic results of an allergic reaction are smooth muscle spasm, edema of the brain coverings and increased glandular secretion. An increase in the spinal fluid or giant urticaria of the brain or its coverings may cause symptoms resembling those of brain tumor. Headache, vomiting, dizziness, failing vision, paresis, convulsions and psychotic changes in the personality are notable symptoms of increased intracranial pressure. Sick headaches may be due to cerebral allergy. Conditions of the optic and auditory nerves, particularly the so-called Ménière syndrome, may be due to neural allergy in children and adults. Peripheral neuritis due to serum sickness may come on twelve to twenty-four hours after injections of tetanus antitoxin, involving the fifth and sixth cervical nerves and causing paralysis lasting from three months to a year; it is sometimes permanent. Prompt recognition and treatment with epinephrine and the intravenous injection of hypertonic solutions of sucrose or dextrose are said to reduce the edema and so relieve the pressure on the nerves.

Two hundred cases of infantile convulsions were studied by J. Thompson in London; he set them down to "anaphylaxis," stating the belief that continuance of the offending diet might lead to epilepsy in later life. Diet affects neural sensitivity in some persons. Cow's milk is prominently mentioned in this respect. The asthmatic child often shows nervous excitability but improves on a change of diet from one too rich in offending proteins.

Clarke says that no allergist suggests that all cases of headache and maladjustment are due to allergy, but that enough of them are to make one consider an allergic condition as a cause. VOORHEES, New York [ARCH. OTOLARYNG.].

CALCINOSIS. FRANK T. MORAN, South. M. J. **40**:840 (Oct.) 1947.

Calcinosis is an infrequent condition characterized by the deposition of calcium salts in the tissues. The origin and pathogenesis are not known. Two patients with the disease are reported on, a 9 year old white boy and a 1 year old Negro girl. Reproductions of roentgenograms accompany the reports. The treatment employed for these patients was not helpful. In neither instance was evidence found of scleroderma, sclerodactylia or Raynaud's disease.

LOGAN, Rochester, Minn.

DERMATOLOGIC PROBLEMS IN THE ALLERGIC CHILD. RALPH BOWEN and MANUEL G. BLOOM, South. M. J. **42**:494 (June) 1949.

This is a good review of the management of eczema in children, though all will not agree with everything which the authors have written. The elimination of skin testing as a means of investigation is wisely pointed out, as is the necessity for maintenance of the infant's nutrition by an adequate diet. Environmental control is often necessary. Treatment of the parents may be as important as that of the infant. Ultraviolet ray treatment is advised but roentgen ray treatment is condemned. The frequent use in these patients of antibiotics and sulfonamides is also condemned. Various prescriptions are given for local use. It is wise to determine blood protein values in infants with severe eczema. Insect bite allergy, miliaria and poison ivy dermatitis are briefly discussed. It is pointed out that in the authors' experience, 50 per cent of children with atopic dermatitis have asthma and 20 per cent of children with asthma give a history of having had infantile eczema.

LOGAN, Rochester, Minn.

ERYTHEMA NODOSUM IN CHILDREN FOLLOWING ADMINISTRATION OF SULPHATHIAZOLE. S. A. DOXIADIS and D. MCLEAN, Arch. Dis. Childhood **23**:273 (Dec.) 1948.

Observations are recorded on 17 children who had erythema nodosum after receiving sulfathiazole. On the basis of clinical, biologic and histologic data, the conclusion is reached that this manifestation is not a "drug rash" due to allergic sensitivity to sulfonamides but is fundamentally the same as erythema nodosum. In order to elicit an eruption of erythema nodosum, sulfathiazole must be given to subjects who are in the active stage of one of the infections commonly associated with spontaneous erythema nodosum. It is, therefore, a provocative and not an etiologic factor. The mechanism of this provocation is unknown.

KELLY, Milwaukee.

CUTIS LAXA. EMLYN LEWIS, Proc. Roy. Soc. Med. **41**:864 (Dec.) 1948.

A case of cutis laxa is reported in a girl, aged 7 years, who was referred to the hospital because of her appearance.

WILLIAMSON, New Orleans.

CONGENITAL MALFORMATIONS OF THE SKIN IN A NEWBORN INFANT. N. GRILLO, Pediatria **57**:86 (Jan.) 1949.

An infant, born at term after a difficult labor, showed serious cutaneous lesions, with ulceration in the abdominal and lumbar regions due to amniotic adhesions.

Penicillin was constantly used to prevent infection of the skin and to permit healthy healing. The child was hospitalized for three months.

HIGGINS, Boston.

HERPES ZOSTER, WITH SPECIAL CONSIDERATION OF POSSIBLE PATHS OF INFECTION. SVEN DAHL, Schweiz. med. Wchnschr. **79**:436 (May 14) 1949.

The author favors the conception that infection in herpes zoster proceeds from the intestinal tract by way of the autonomic nervous system.

AMBERG, Rochester, Minn.

## Surgery and Orthopedics

ESSENTIAL PES CAVUS: LATE OPERATIVE CONTROLS. ARTURO COFRE, Arch. d. Hosp. niños Roberto del Rio **16**:61 (June) 1948.

The author reports 5 cases of tenotomies performed for pes cavus. All children were operated on early in life. Two had recurrences, and in the rest of the patients there remained a slight tendency toward talipes varus. It is the conclusion of the author that such operations should be postponed until the age of 11 or 12 years.

MILLER, Newark, Ohio.

## Teeth and Dentistry

MODERN DRUGS IN DENTAL SURGERY. WALTER J. DILLING, Proc. Roy. Soc. Med. **43**: 53, (Jan.) 1950.

The pharmacology and therapeutics of those drugs which have proved to be of definite value in dentistry are discussed. A plea is made for discarding those drugs of dubious effectiveness, including arsenic, iodoform and certain of the proprietary preparations, in favor of those of definite value. In the latter group the following drugs are recommended: hydrogen and zinc peroxides, sodium hypochlorite, iodine, formaldehyde and oxymethylene (paraform), zinc sulfate, alcohol, phenol, cresol, chlorocresol or chlorozylenol, clove oil, thymol, one surface-reducing agent, proflavine, methylrosaniline chloride, sulfonamides, penicillin and streptomycin.

HEARD, Monterey, Calif.

## Miscellaneous

THE EXPERIMENTAL AND CLINICAL USE OF POLYMYXIN, CHLOROMYCETIN, AND AUREOMYCIN. PERRIN H. LONG, EMANUEL B. SCHOENBACH, ELEANOR A. BLISS, MORTON S. BRYER and CAROLINE A. CHANDLER, California Med. **70**:157 (March) 1949.

Polymyxin is an effective antibiotic for the treatment of severe infections produced by Pseudomonas aeruginosa, Hemophilus pertussis, Hemophilus influenzae, Escherichia coli and Aerobacter aerogenes. Its toxicity to date precludes its general use in infections susceptible to its therapeutic effects.

Chloramphenicol (chloromycetin®) has been demonstrated to be an effective antibiotic agent for the treatment of rickettsial diseases and typhoid. It will undoubtedly prove effective in the treatment of other infections produced by certain gram-negative micro-organisms and viral agents.

Aureomycin has been shown to be an active antibiotic agent against rickettsial diseases, primary atypical pneumonia, acute brucellosis, pneumococcic, streptococcic

and staphylococcic infections, urinary tract infections produced by E. coli, A. aerogenes and Streptococcus faecalis, certain types of infections of the eye and subacute bacterial endocarditis when the infecting agent is Str. faecalis. Its clinical use in forms of extrapulmonary tuberculosis is in a completely experimental stage. It is not recommended in therapy of typhoid or in infections due to Ps. aeruginosa or Proteus vulgaris, and it seems to be ineffective in treatment of whooping cough. To date, neither chloramphenicol nor aureomycin has shown significant signs of systemic toxicity.

PRYOR, Redwood City, Calif.

SUDDEN AND UNEXPECTED NATURAL DEATH: IV. SUDDEN AND UNEXPECTED NATURAL DEATH IN INFANTS AND YOUNG CHILDREN. S. M. RABSON, J. Pediat. **34**:166 (Feb.) 1949.

Sudden and unexpected natural death in children occurs chiefly in boys, and seldom after the age of 3 years. Almost 80 per cent of the infant deaths in Rabson's report were caused by respiratory disease. In some infants, particularly in the 4 to 8 month age group, present methods of investigation may not uncover the cause of death. The role of the thymus in sudden death has yet to be clarified. Death from obstructive pressure of an enlarged thymus is rare.

MACDONALD, Pittsburgh.

A SIMPLIFIED INFUSION SET FOR INFANTS. MACK SUTTON, Pediatrics **3**:423 (April) 1949.

This set can be made of easily obtained parts and has proved practical and convenient for routine use, especially with infants. This paper includes complete instructions for constructing and using the set.

FROM THE AUTHOR'S SUMMARY.

A COMMENTARY ON NATURAL CHILDBIRTH. FREDERICK W. GOODRICH and HERBERT THOMS, Pediatrics **3**:613 (May) 1949.

Obvious psychologic advantages of a rooming-in plan lead the obstetrician to consider the emotional aspects of childbirth and to ask whether labor and delivery are emotionally satisfactory for a mother in the culture of today. The usual emphasis in caring for the parturient woman has been largely on the satisfaction of her somatic needs, often to the neglect of her psychic needs. Dr. Grantly Dick Read has pointed out that the fears present in most pregnant women can be the cause of pain in labor and that if these fears can be obliterated by education and sympathetic attention during labor women are enabled to go through delivery without undue discomfort and without the necessity for the use of deep analgesia and anesthesia. Furthermore, these mothers will find that childbirth is an emotionally satisfying experience.

Applying the philosophy and technics suggested by Dr. Read to a group of patients in this clinic, we have found that this is true. Our patients, in addition to the usual prenatal care, are given lectures on the anatomy and physiology of pregnancy, labor and delivery and are taught a few simple exercises designed to enhance their ability to relax. In addition, these patients are closely attended during labor by members of the medical and nursing staffs. A majority of these women are thus enabled to be conscious at delivery and to experience the emotional reaction which is so satisfying and which manifestly establishes a desirable mother-child relationship at the beginning of the infant's life.

A statistical analysis of the results of this study will appear in another communication. However, results are convincing that these technics are physically safe and psychologically desirable for most pregnant women.

FROM THE AUTHORS' SUMMARY.

THE CLINICAL INTERPRETATION OF STERNAL PUNCTURE. PAUL L. BEDINGER and LOUIS A. LIMARZI, Illinois M. J. **94**:351 (Dec.) 1948.

A discussion on the technics and interpretations of the observations on sternal punctures in health and disease is presented. The article is too detailed for an adequate abstract.

BARBOUR, Peoria, Ill.

INHIBITION OF ANAPHYLACTIC SHOCK BY ACETYLSALICYLIC ACID. BERRY CAMPBELL, Science **108**:478 (Oct. 29) 1948.

Shock, nonfatal in most of the animals, was produced in rabbits by repeated intravenous injections of egg white. Acetylsalicylic acid in doses of 5 grains (0.32 Gm.) daily for three days prior to the shocking dose prevented the appearance of typical symptoms. When retested three weeks later without further administration of acetylsalicylic acid, typical shock was produced. The drug failed to prevent the appearance of fatal histamine (2.75 mg. intravenously) shock.

FORBES, St. Louis.

SUDDEN DEATH IN INFANCY (A PRELIMINARY COMMUNICATION). LESLIE L. R. WHITE, Proc. Roy. Soc. Med. **41**:866 (Dec.) 1948.

A preliminary study of the autopsy observations in 81 cases of sudden death in infancy is presented. Of 30 deaths suspected from circumstantial evidence as due to overlaying, 9 were the result of mechanical suffocation; the remaining 21 were ascribable to other causes. Asphyxia due to aspiration of regurgitated food as a cause of death is discussed.

FROM THE AUTHOR'S SUMMARY.

NITRATE POISONING FROM WELL WATER. N. S. B. MCLETCHIE and H. E. ROBERTSON, Canad. M. A. J. **60**:230 (March) 1949.

Two deaths in 6 weeks old infants were attributed to ingestion of well water containing nitrates. A survey of rural wells in Saskatchewan revealed what is considered a dangerously high nitrate content in 25.5 per cent. The source of the nitrates was apparently bacterial decomposition of animal excreta in most cases.

MCGUIGAN, Evanston, Ill.

RELATION BETWEEN CONCENTRATIONS OF PENICILLIN IN THE BLOOD AND IN THE SPINAL FLUID. MARIA GOMIRATO SANDRUCCI, Minerva pediat. **1**:17 (Jan.) 1949.

The object of this study was to determine when and if penicillin would pass from the blood to the spinal fluid and vice versa. In the first year of life penicillin may pass from the blood to the spinal fluid in small amounts, but thereafter there appears to be an impenetrable barrier to such passage when there is no meningeal irritation. In patients with meningeal lesions, penicillin will pass from the blood to the spinal fluid; the greater the amount of protein in the spinal fluid, the greater the amount of penicillin passing into it. The amount of penicillin passing from the blood to the spinal fluid is greater in persons with tuberculous meningitis than in those with purulent meningitis and still greater than in those with nonbacterial

meningitis or encephalopathies. Intrathecal injection of horse serum induces the passage of some penicillin from the blood to the spinal fluid. The amount of penicillin passing from the spinal fluid to the blood is governed by the same conditions as regulate the passage in the reverse direction. HIGGINS, Boston.

TOXICITY OF STREPTOMYCIN. C. FUA, Minerva pediat. **1**:43 (Jan.) 1949.

Fua gives his personal experience in regard to the toxicity of streptomycin from his treatment of 47 patients with tuberculosis, several of them with meningeal involvement. He cautions against the use of amounts greater than 0.1 Gm. in a single intrathecal injection. HIGGINS, Boston.

FATAL LEAD INTOXICATION IN A TWELVE WEEK OLD BREAST-FED INFANT. HANS-RUDOLF WIEDEMANN, Arch. f. Kinderh. **133**:7, 1946.

A 12 week old girl was admitted to the hospital with opisthotonos, bulging fontanel and other typical signs of meningitis. The spinal fluid showed web formation. Excessive basophilic stippling of the erythrocytes and heavy metal lines in the roentgenograms of the long bones confirmed the diagnosis of lead intoxication (cerebromeningeal type). Death occurred on the following day. Pathologically, high values for lead were demonstrated by chemical analysis of cerebral, hepatic and renal tissue and in the ash of the bones obtained at autopsy.

A catamnestic search for the cause of the lead intoxication revealed that, because of soreness, a thick layer of ointment of lead oleate N. F. had been applied to the nipples after each breast feeding. It had been ordered that the ointment be removed with alcohol before the next breast feeding. ARON, Chicago.

USES AND DOSAGE OF PENICILLIN IN PEDIATRICS. E. GRUNDLER, Arch. f. Kinderh. **133**:34, 1946.

Since penicillin was extremely scarce in Germany, the doses recommended and used were small, if not minimal, 1,000 units intramuscularly every three hours, a total of 8,000 units per day for three to five days. It is remarkable to learn that with this dosage surprisingly favorable results were achieved in 2 infants with extended cellulitis and in 3 other infants with bronchopneumonia and pleuritis proved to be sulfonamide resistant. The author emphasizes that the infants could not have been saved without the penicillin therapy. ARON, Chicago.

THERAPEUTIC EFFECTS OF PENICILLIN IN TWO HUNDRED CHILDREN. N. URBAN, Med. Klin. **44**:13 (Jan. 7) 1949.

Penicillin therapy was instituted in children with infantile bronchopneumonia, pleural empyema, sepsis, meningitis, pertussis pneumonia, atypical bronchopneumonia, pyoderma, phlegmon and other diseases. The beneficial effect in a number of the children has been confirmed. AMBERG, Rochester, Minn.

ANILINE INTOXICATION IN INFANTS. ALEXANDER SINIOS, Med. Klin. **44**:114 (Jan. 28) 1949.

Ten infants, 4 weeks to 5 months old, became pale and cyanotic on the same day. New, not yet washed, diapers had been used to protect the upper end of the bedsheet. They had been stamped with a dye containing aniline bases. The cyanosis disappeared shortly after removal of the diapers.

AMBERG, Rochester, Minn.

HISTAMINE GIVEN INTRADERMALLY AS AN ANALGESIC. O. DUB, Schweiz. med. Wchnschr. **79**:293 (April 2) 1949.

As closely as possible to the localization of the pain 0.1 cc. of a 0.1 per cent solution of histamine chlorhydrate is injected intradermally. Up to twenty such injections may be given. There may be some disagreeable symptoms but no severe ones were observed. The amount of the injections in a given region is increased gradually to 0.2 and 0.3 cc. Patients with spondylarthritis were treated, as well as those with monarthritis and polyarthritis and a number of various other painful ailments, such as radiculitis and chronic headache. In many patients the pain was relieved to a greater or less extent.

AMBERG, Rochester, Minn.

ANILINE POISONING IN A CHILD. E. JOSEFSSON, Nord. med. (Hygiea) **29**:243 (Feb. 1) 1946.

A report is given of a case of aniline poisoning in a boy aged 17 months. He was found sucking on an aniline pen. When he was examined two hours later, the mucous membrane of the mouth was discolored by aniline. He was immediately given a gastric lavage; the lavage water from the stomach was blue. One hour later he became drowsy and was unconscious. There was no cyanosis but he was pale. Convulsions followed. Methemoglobin was demonstrated in the blood. During a blood transfusion he had an eclamptic attack and died shortly afterward. At the postmortem examination an intense edema of the brain was demonstrated as the most striking sign. The author discusses the syndrome in this case. He finds no reason to believe that the death was due to incompatibility of the transfused blood and maintains that the morbid clinical signs were caused by acute aniline poisoning.

WALLGREN, Stockholm, Sweden.

POISONING THROUGH METALDEHYDE (META-TABLET®). LARS-ERIK CARLGREN, Svenska läk.-tidning. **43**:52 (Jan. 4) 1946.

A girl, 2 years old, became ill a few hours after eating probably only 0.5 Gm. of a preparation of metaldehyde (meta-tablet®). She was pale and drowsy, and had intermittent chills. The tendon reflexes were normal; the pulse rate was 125. On gastric lavage acetaldehyde was demonstrated. Next day she still was somewhat dull and displayed unsteady gait, with subsequent rapid recovery. This is the third case of poisoning with meta-tablets® from Sweden; the other 2 were published by Belfrage and Ingolf.

WALLGREN, Stockholm, Sweden.

ANILINE INTOXICATION IN A WARD FOR INFANTS. ERNST RASMUSSEN, Ugesk. f. læger **108**:1212 (Oct. 31) 1946.

The new diapers for the ward had been marked with aniline dye, which was dried by putting the diapers on a central heating element in the nursery. All 8 infants in the ward, aged 9 days to 3 months, became cyanotic, some of them only on the lips. Others had a general bluishness of the skin. Hemoglobin was demonstrated in the urine. The children displayed no other signs of sickness, and the cyanosis disappeared within five days. One of the infants, who had congenital heart disease, died two days after the intoxication, probably from heart failure.

WALLGREN, Stockholm, Sweden.

# Society Transactions

## SOCIETY FOR PEDIATRIC RESEARCH

**Francis F. Schwentker, M.D., *President***

***Twentieth Annual Meeting, French Lick, Ind., May 8 and 9, 1950***

**First Session**

***Monday Morning, May 8***

**Isolation of a Filtrable Agent from Throat Washings Collected During an Outbreak of Epidemic Pleurodynia.** Dr. T. H. Weller, Dr. J. F. Enders, Dr. A. M. Pappenheimer, Dr. M. Buckingham and Dr. J. J. Finn, Boston.

In 1947 an outbreak of epidemic pleurodynia occurred in the Boston area. No etiologic agent could be isolated at the time. Recent reports in the literature describing the isolation of the Coxsackie group of viruses from patients with so-called "nonparalytic poliomyelitis," as well as from a patient with a diagnosis of sporadic epidemic pleurodynia, have stimulated a reinvestigation of material collected during the 1947 outbreak. By intracerebral inoculation of throat washings into newborn mice a filtrable agent has been isolated from each of 4 patients with epidemic pleurodynia. Two of these agents, termed the DeMole and Kine viruses, have been studied in detail. The inoculation of 100 median lethal doses into mice of less than 30 hours of age produces death in three to six days. In such mice pathologic examination reveals hepatitis and occasionally pancreatitis. With increasing age mice rapidly develop resistance to the agents.

Neutralization tests carried out with the DeMole and Kine agents and their respective serums showed that during the course of the illness the patients developed neutralizing antibodies against their own virus. In addition, the development of neutralizing antibodies against both the Kine and DeMole viruses was conclusively demonstrated in the serums of 5 other patients with epidemic pleurodynia.

Additional evidence that these agents were etiologically related to the outbreak was provided by the results of experiments demonstrating that the DeMole virus could be reisolated from throat washings but not from the same washings after they were heated at 65 C.

The possible relation of the DeMole virus to certain members of the Coxsackie group was investigated. By cross neutralization and cross protection tests on mice immunized transplacentally an immunologic relation was demonstrated between the DeMole virus and the Connecticut 5 strain of virus originally isolated by Melnick, Curnen and their associates from a patient with "nonparalytic poliomyelitis." Certain epidemiologic observations suggest that different strains of this group of viruses, although immunologically related, may vary in their pathogenic potentialities and that the predominant clinical picture may be determined by the strain involved.

**Evidence for Newcastle Disease Infection in Man.** Dr. Frederick B. Bang and Dr. David T. Karzon, Baltimore.

Although the Newcastle disease virus (NDV) is well known as the cause of pneumoencephalitis in chickens, only recently has it been considered as a cause of

disease in human beings. Isolation of the virus has proved it to be the causal agent of a benign conjunctivitis in man. Furthermore, the discovery in fresh human serums of a substance which inactivates the virus in chick embryo neutralization tests has given the impression that it may also produce a generalized systemic human infection. Since the evidence for such systemic invasion rests entirely on the diagnostic significance of the neutralization test, we were led in the present study to analyze more closely the kinetics of the NDV neutralization procedure.

There appears to be universally present in human serums a thermolabile component, not complement, which inactivates up to 100,000 embryo-infective doses of NDV. This component differs from chicken convalescent antibody in the following important ways.

1. The human heat-labile factor is completely inactivated when heated to 56 C. for ten minutes, and it loses most of its activity within two weeks when kept at 4 C. Chicken antibody is not destroyed when heated at 56 C. for thirty minutes and will remain active indefinitely at 4 C.

2. The slope of the neutralization curve is steeper for the human serum component, that is, falls more rapidly with dilution of serum (slope of 4.0 for human serum component and slope of 1.0 for the chicken immune serum).

3. To demonstrate viral inhibition with the human serum component incubation of the virus-serum mixture in vitro is required prior to inoculation into the host. Maximal inhibition is obtained when the mixture is held at 35 C. for one hour. Neutralization by chicken immune serum does not depend on virus-antibody contact in vitro.

Knowledge of these variables provided a feasible method for the study of NDV-neutralizing substances and a possible correlation with clinical entities. Utilizing this procedure, we found that the paired serums from 3 patients with NDV conjunctivitis showed no rise in heat-labile or heat-stable neutralizing substance. In reviewing all available data, we feel that there is no conclusive evidence that NDV causes a systemic infection of man. That suggestion cannot be ruled out, however, since one worker in our laboratory was found to have a significant titer of a heat-stable neutralizing substance consistently over a two year period though he had no recognizable clinical illness.

On a broader aspect of this problem, the nonspecific heat-labile substance which is present in most mammalian species and which we demonstrated in 24 of 24 fresh unheated human serums, including 4 infants, may represent a species characteristic rather than a response to an antigen.

**Some Quantitative Aspects of Infant Immunology.** Dr. John J. Osborn, Dr. Joseph Dancis and Dr. Juan Julia, New York.

Several aspects of the immunology of the premature and newborn infant were studied quantitatively with use of the relatively accurate method of titration of diphtheria antitoxin by the rabbit Schick test and of tetanus antitoxin by the mouse protection test.

1. *Passive Transfer.*—It is generally accepted that an infant at birth has roughly the same concentration of circulating antibodies as his mother. It has been suggested that the premature infant may not receive the same amount of passive antibody because of incomplete placental transfer. To obtain data on the permeability of the placenta to maternal antibody in the months before term we studied 27 premature infants. These ranged in birth weight from 600 to 2,400 Gm. All were the children of mothers with high levels of diphtheria antitoxin. The antitoxin titer of the cord blood was compared with that in the maternal blood.

In only 4 of 15 infants with a birth weight over 1,600 Gm. were the cord antitoxin levels below those of the mother. In 10 of 12 infants with birth weights under 1,600 Gm. the cord blood antitoxin levels were substantially below the mothers' levels. These results suggest that the placenta may not be so permeable to maternal antibody earlier in gestation as it is at term.

2. *Active Immunization.*—Most previous workers studying active immunization of the infant have used a series of two or three monthly immunizations. As a result they have usually not measured the response during the newborn period, and their results reflect both the primary and the booster responses. To obtain more quantitative results for the newborn period two standard antigens were prepared, one containing 100 L.F.D. (least fatal doses) of diphtheria toxoid on alum and the other 163 L.F.D. of tetanus toxoid on alum. (These represent approximately equivalent amounts of antigenic protein for the two substances.) Forty-five infants, ranging in age from newborn through 6 months, were immunized with a single dose of diphtheria toxoid, and 20 infants also received tetanus toxoid. Antibody titers were determined for each child at several intervals up to six months after immunization. The resulting curves of antibody response showed that older infants (over 2 months) formed antibody faster and in greater quantity than infants 1 month old or younger. The response to diphtheria toxoid and tetanus toxoid was qualitatively the same; however, measurable amounts of tetanus antitoxin could be detected earlier than diphtheria antitoxin in all age groups.

3. *Interference by Passive Antibody.*—The effect of passively received (transplacental) maternal antibody on active immunization of the infant was studied. As a rule, in infants with circulating passive (maternal) antitoxin shortly after immunization with toxoid the antibody level fell below measurable levels. If the level of passively received antibodies was low, this rapid fall was followed by a secondary rise indicating active immunization. In several infants in whom the level of passively received antibodies was high the secondary rise did not appear. Instead, the antibody titer remained below measurable levels for six months after the primary immunization. However, a second injection of toxoid at this time produced an immediate booster response, indicating that these infants, too, had received some degree of active immunization from the first dose.

**The Relation of Antibody Production to the Development of Rheumatic Fever.** Dr. Floyd W. Denny, Hartsville, S. C., Dr. Lewis W. Wannamaker, St. Matthews, S. C., and Dr. Charles H. Rammelkamp, Cleveland.

Because numerous observations have indicated that the serum of patients with rheumatic fever exhibit high streptococcic antibody titers, a study was undertaken to define this relation more adequately. For this purpose antistreptolysin "O" determinations were made by an accurate method on acute and convalescent serums collected from 643 patients with acute streptococcic infections. Of this group 25 subsequently manifested rheumatic fever. There were an additional 77 persons with acute rheumatic fever observed but not included in the studied group.

Analysis of the data showed that both the initial and the convalescent titers of the patients in whom rheumatic fever subsequently develops are higher than the titers of persons recovering from streptococcic disease in whom rheumatic fever does not develop.

The patients were then divided into three gorups: those whose serum showed (1) low, (2) medium and (3) high initial antistreptolysin titers. Each of these groups could be subdivided into those who had small and large antibody responses following the streptococcic illness. Such analyses showed a marked difference

in the attack rate of acute rheumatic fever. In groups 1 and 2 of low and medium initial titers, in which little antibody developed, the rates for rheumatic fever were low, being 1.18 per cent and 1.76 per cent respectively. In contrast, in these same two groups when the antistreptolysin response was great the values increased to 5.95 and 13.33 per cent. In the group in which the initial titers were high (group 3) but the response low, the rate was 10.34 per cent.

These data establish that persons whose antibody repsonse is maximal are especially liable to development of rheumatic fever. This type of response is apparently related, in part, to previous experience of the host with the streptococcus, as indicated by the high antibody titers obtained during the acute phase of the initiating infection. These observations have important implications concerning the inherent mechanisms responsible for the development of rheumatic fever.

**Effect of Triethylene Glycol Vapor and Dust-Suppressive Measures on the Respiratory Cross Infection Rate of an Infants' Ward.** Dr. Saul Krugman and Dr. Robert Ward, New York.

This study was conducted in two identical infants' wards—one with and one without glycol vapor. During the first part of the investigation, from February 1949 to May 1949, only triethylene glycol vapor was used in the test ward; no dust-suppressive measures were used. Data were collected on 59 patients who spent 2,020 hospital days in the test ward and 71 patients who stayed for a total 2,150 days in the control ward. The results of this part of the study indicated that there were 31 cross infections in the control ward as compared with 10 in the test ward; the rate per 1,000 patient hospital days was 14.4 and 4.95 respectively. Measles developed in 6 patients in the control ward after three separate accidental exposures. On four different occasions patients in the glycol ward were exposed to measles with no resulting cross infections.

During the second part of the study, from December 1949 to May 1950, both triethylene glycol vapor and dust-suppressive measures were employed. Data were collected on 52 patients who spent 2,125 hospital days in the test ward and 63 patients who stayed 2,011 days in the control ward. At the conclusion of this part of the study there were 13 cross infections in the control ward as compared with 20 in the test ward. The rate per 1,000 patient hospital days was 6.5 and 9.4 respectively.

During 1949 the cross infection rate of the glycol ward was significantly lower than that of the control ward. During the 1950 study, however, the cross infection rate of the glycol ward was slightly higher than that of the control ward. Under the conditions of our experiments and on the basis of the combined 1949-1950 study, there was no significant difference in the cross infection rate of the glycol ward as compared with that of the control ward.

**A Single, Simple Turbidimetric Method for the Assay of Aureomycin, Chloramphenicol, Penicillin, Streptomycin and Terramycin in Capillary Blood and Other Body Fluids.** Dr. Coleman M. Whitlock Jr., Dr. Andrew D. Hunt Jr. and Dr. Sylvia G. Tashman, Philadelphia.

A single turbidimetric method of bioassay that is demonstrably accurate in the presence of various body fluids for the five antibiotics listed in the title is described. The test organism is a strain of Staphylococcus aureus. The growth of the organism in various known concentrations of the antibiotic being assayed is measured turbidimetrically, and the value obtained is subtracted from the

turbidimetric value for free growth of the organism. The resulting values are squared, and a standard curve is plotted. Unknown solutions are run simultaneously under the same conditions of assay, and the turbidimetric values obtained are also subtracted from the figure for free growth of the organism. The resulting values are squared, and the concentration of antibiotic in the unknown specimens is then read from the standard curve.

The method has been found accurate for the assay of all five of the antibiotics in human serum, urine and cerebrospinal fluid. Representative of this accuracy are the figures for aureomycin assay: (1) in serum, an average percentage error of 8.3, with a range of error from 0 to 35; (2) in spinal fluid, an average percentage error of 12.3 and a range of 0 to 35 and (3) in urine, an average percentage error of 12.4 and a range of 0 to 42. The method is only about half as accurate as when aureomycin is assayed, when chloramphenicol is assayed in cerebrospinal fluid, when streptomycin is assayed in urine and cerebrospinal fluid and when penicillin and terramycin are assayed in all three body fluids.

The method is technically simple. Results are obtained in four hours. Small volumes of unknown solutions are required for assay, and low concentrations of antibiotic are detectable. This method is used for all antibiotic assay in our laboratory and is peculiarly suited to pediatric practice.

**Studies on Fat and Vitamin A Absorption in Premature Infants.** Dr. Soledad M. Morales, Dr. Arthur W. Chung, Dr. Jacques Lewis and Dr. L. Emmett Holt Jr., New York.

Our studies were directed mainly toward the improvement of the defective state of fat absorption that is found in premature infants. Investigations by Tidwell and Holt, Gordon and McNamara and Gordon and Levine have demonstrated this defect in fat absorption in such infants. Tidwell and Holt showed that the average retention of butter fat by premature infants was 65 to 70 per cent of the intake and often less, as contrasted with 85 to 95 per cent retention by full term infants.

Our first study was undertaken to ascertain whether the same principle of fat absorption found in steatorrheas associated with cystic fibrosis of the pancreas and celiac syndrome, in which, as reported by Chung and Holt recently, the fat intake was directly related to the quantity of fat provided in the diet, held for the steatorrhea found in the premature infant. We obtained data on the retention of fat by 8 healthy premature infants following the administration of low and high fat diets. At the same time we also ascertained the effect of low and high fat diets on the vitamin A excretion of the same infants. Our results indicate that the percentage of fat intake retained by the premature infant is the same whether the fat is administered in low or high amounts, and, thus, increasing the quantity of fat in the diet results in a correspondingly larger net absorption of fat. Therefore, the same principle of fat absorption holds for the premature infant as for the infant with cystic fibrosis of the pancreas and celiac syndrome. The data obtained on the absorption of vitamin A following the administration of low and high fat diets showed clearly that the high fat feedings had no deleterious effect on its absorption.

The finding that relatively high fat diets given to premature infants not only result in better retention but are also well borne clinically suggests that the currently advocated restriction of fat for these infants is unnecessary.

Our next study was to determine the effect of particle size of fat and vitamin A on their absorption in premature infants. Six healthy premature infants were studied on three experimental periods of four days each. The diet in all three

periods was the same from the standpoint of percentage of fat fed, the number of calories given and the amount of vitamin A administered. The only difference was that the butter fat and fish liver oil preparations were administered in an emulsified state in milk during periods 1 and 3, whereas during period 2 they were given separately in an unemulsified form.

In all of the 6 premature infants, the absorption of butter fat was much better when it was emulsified than when it was given in an unemulsified state, the average absorption of emulsified butter fat being 71.5 per cent and of unemulsified butter fat only 40 per cent. Similarly, the absorption of vitamin A was found to be definitely superior when the fish liver oil preparation was emulsified in milk. The average retention of vitamin A given in the emulsified state was 63 per cent, whereas when given unemulsified the absorption was only 43 per cent.

The results of this investigation clearly indicate that particle size plays an important role in the absorption of fat and vitamin A in the premature infant. The beneficial effect of homogenization as compared with use of an unemulsified preparation is striking.

Lastly, we tried to determine the effect of an emulsifying agent on fat and vitamin A absorption in premature infants. Certain substances commonly known as tweens have been developed commercially as emulsifying agents, their emulsifying and wetting property being attributed to their ability to lower surface tension. (The tweens comprise a series of polyoxyalkylene derivatives of hexitol anhydride partial long chain fatty acid esters.) We chose two of these substances, tween 80® and tween G1205,® for our study. Seventeen premature infants were studied in all. The average gain in fat absorption was 6 per cent with tween 80® and 13.1 per cent with tween G1205.® The average percentage gain of absorption of vitamin A with both tweens was more striking than that of fat, being 16 per cent. The data are strongly suggestive of the effectiveness of tweens in improving fat and vitamin A absorption in premature infants.

**Effect of Strong Iodine Solution U. S. P. (Lugol's Solution) on Thyroid Function as Measured by Radioactive Iodine Uptakes.** Dr. Lyon Oettinger, Jr. and Dr. Amelia Frances Wheelwright, Los Angeles.

Strong iodine solution U. S. P. (Lugol's solution) has long been used in the treatment of thyroid diseases and in the preparation of the hyperthyroid patient for surgery. The amount needed to obtain the maximum effect desired and the duration of this effect after administration of the drug was stopped have been very difficult to determine. The introduction of radioiodine in 1937 gave us a tool with which a better estimate of the effect of the solution could be made.

In this investigation we have attempted to determine both the minimum amount of the drug required to give maximum depression of thyroid function and the duration of this effect.

To determine how much drug is needed to achieve maximum depression of thyroid function strong iodine solution U. S. P. was given for ten days to hospital normal children and normal medical students. The daily doses were 0, 2, 4, 8 and 16 drops. Iodine uptake studies were done the day before administration of the solution was started and the day after it was completed. This was done on the hypothesis that a measure of the absorption of iodine from the blood stream in the absence of drugs such as thiourea and sulfonamides would be a measure of thyroid function. At the conclusion of the work it was found that even so small an amount as 2 drops of the solution a day had a marked depressant effect on the thyroid gland and 8 to 16 drops a day achieved maximum depression.

After collection of the active data another group of persons was given 10 drops of strong iodine solution a day for ten days, and the iodine uptakes were measured before the start of the administration of the drug and at one, three, five, seven, fourteen and twenty-one days after the drug was no longer given. At the end of three days there was a marked return of function, and at five days the absorption of iodine seemed to be perfectly normal.

These findings would not serve as a standard for hyperthyroid patients in whom strong iodine solution causes involution of the acinar cells as well as a simple blocking of the absorptive function.

It is concluded from this study that in hospital normal children and healthy young adults 8 to 16 drops of strong iodine solution U. S. P. will cause maximum depression of thyroid function as measured by iodine uptake. This depression persists for only a short time after use of the drug is stopped, and the uptake returns to a normal value within five days.

## Second Session

### *Monday Afternoon, May 8*

**Changes in Blood Volume in the Neonatal Period.** Dr. Gladys J. Fashena, Dr. Harriet H. Bates and Dr. Allan F. Reid, Dallas, Texas.

The volumes of circulating whole blood, red cells and plasma were determined by the radioactive phosphorous technic for 41 normal infants, a few hours after birth and again at 1 week of age. Simultaneous red cell counts, packed red cell volumes and serum bilirubin levels were obtained. The mean whole blood volume was 94.9 ± 17.2 cc. per kilogram (range 55 to 152 cc. per kilogram) at birth and 95.3 ± 14.2 cc. per kilogram (range 72 to 128 cc. per kilogram) at one week. Mean red cell volumes were 54.1 ± 11.0 cc. per kilogram (range 31 to 77 cc. per kilogram) and 48.1 ± 9.2 cc. per kilogram (range 32 to 68 cc. per kilogram) at birth and one week respectively. Mean plasma volume at birth was 40.8 ± 9.8 cc. per kilogram (range 23 to 78 cc. per kilogram) and at one week 47.2 ± 8.3 cc. per kilogram (range 32 to 73 cc. per kilogram). Thus, although the mean circulating whole blood volume per kilogram for the group was essentially the same at the two ages, the mean red cell volume showed a decrement of 12 per cent and the mean plasma volume an increment of 13 per cent at 1 week of age.

The variability of pattern among individual infants was striking. Three fourths of the subjects exhibited drops in red cell volume of varying degree, but one fourth showed net red cell increments at the age of 1 week. Plasma volume increments occurred in 88 per cent of the subjects; the magnitude of the change appeared to be independent of the changes in red cell volume. Certain infants showed marked changes in red cell volume without appreciable plasma volume change, whereas others maintained approximately the same red cell volume but exhibited gross changes in plasma volume. Thus, the drop in red cell count and hematocrit which occurs in the neonatal period is shown to be the resultant of two factors: absolute changes in red cell mass and hemodilution due to plasma volume increase. The determination of red cell count or packed red cell volume gives no clue as to which factor may be operating in a given patient. No correlation was observed between the magnitude of red cell volume decrements and the degree of hyperbilirubinemia observed at birth and at one week of age. This confirms previous work which has shown that neonatal hyperbilirubinemia is primarily a function of hepatic immaturity.

All the volume changes observed in this study must be interpreted in the light of the fact that volumes of circulating fluid only can be measured. What part inactive reservoirs of blood may play is a matter for conjecture.

**Study of Oxygen Saturation of Arterial Blood of Normal Newborn Infants by Means of a Modified Photoelectric Oximeter.** Dr. Elmer L. Crehan, Dr. Roger L. Kennedy and Dr. Earl H. Wood, Rochester, Minn.

A photoelectric oximeter suitable for use on newborn infants was used to determine the arterial oxygen saturation of 102 normal newborn infants. This instrument made possible bloodless, painless and continuous determination of oxygen saturation by means of an earpiece attached to the pinna of the heat-flushed ear.

The earpiece was calibrated on 26 normal adult subjects. In the range of saturation of more than 90 per cent the standard deviation of the difference between simultaneous determinations made by Van Slyke analyses of arterial blood and the ear oximeter was ± 2.9 per cent saturation. The range of variability increased with decreasing saturations so that in the range from 55.0 to 65.0 per cent the standard deviation was ± 9.2 per cent saturation.

The arterial oxygen saturation was determined almost continuously for 18 infants during the period that they were from 3 minutes to 2 hours of age. The average oxygen saturation of these infants at 5 minutes of age was 67.1 per cent (range 31 to 92). This value had increased to 89 per cent (range 64 to 100) at 17 minutes and to 94.3 per cent (range 90 to 99) two hours after birth.

The rapidity of the increase in oxygen saturation during the immediate neonatal period varied from infant to infant and was apparently related to the time of onset and vigor of the initial respiratory effort.

Studies were conducted on 84 infants varying in age from 3 hours to 7 days. These subjects were divided according to age into eight groups. The average arterial saturation of the infants in the various age groups during the first week of life fell within the range of individual values found in normal adults. Single determinations, however, frequently fell below the normal range for adults.

The results obtained tend to show that under the conditions of these studies normal newborn infants, although very hypoxemic at birth, have a rapid increase in the oxygen saturation of arterial blood so that at 17 minutes of age the average values fall within the range of individual values obtained in adults. The studies carried out during the first seven days after birth indicated that transient decreases in arterial saturation to values below the range obtained for normal adults frequently occurred, especially when the infants were sleeping or resting quietly. Spontaneous recovery to the normal range of saturation regularly occurred when the infants awakened or were startled.

That these transient decreases in oxygen saturation were probably pulmonary in origin and that the values obtained by the infant oximeter were reasonably accurate is indicated by the fact that the arterial saturation readings uniformly increased to values not significantly different from 100 per cent when the infants were exposed to an atmosphere containing 90 per cent oxygen.

**Oxygen Content of the Blood at Birth.** By Dr. Bertram R. Girdany, Dr. Yolanda DiCastro and Dr. David McL. Greeley, New York.

Measurements of the oxygen content of cord blood and also of the capillary arterial blood at five, ten, thirty and sixty minutes after birth were made on 229 infants.

The modal value of oxygen content of cord blood was 8 volumes per cent; at five minutes the value for capillary arterial blood was 5 volumes per cent; at ten minutes, 14 volumes per cent; at thirty minutes, 18 volumes per cent, and at one hour, 20 volumes per cent. No statistically significant difference was noted in the capillary arterial blood oxygen of infants at these various time intervals which could be correlated with the following obstetric factors: (1) use of a barbiturate premedication; (2) use of local, caudal, spinal or cyclopropane anesthesia as compared with nitrous oxide-oxygen and ether, anesthesia; (3) delivery by cesarian section, and (4) encirclement of the neck by the umbilical cord.

Only 13 of the 229 infants had a capillary arterial oxygen content of 18 volumes per cent or less at 1 hour of life. One of these infants died, 3 were premature, 9 required special measures for resuscitation and 4 were apparently normal.

This report is part of a study the primary purpose of which is a correlation of later mental and physical growth with the oxygen content during the minutes following birth.

**Spirometry as a Means for Studying Ventilatory Function of Patients in Mechanical Respirators.** Dr. Clifford G. Grulee, Jr., Dr. Frederic L. Eldridge and Dr. G. David Ford, Galveston, Texas.

The question of placement in the respirator and regulation of the respirator remains one of the chief problems in the ventilatory deficiency associated with poliomyelitis. To aid in its solution a standard basal metabolism apparatus was converted for use as a recording spirometer by means of a mask or an attachment to a tracheotomy tube. This offered a simple method for determining respiratory adequacy in various types of ventilatory deficiency by comparing minute volumes so obtained with standard values. The general availability, technical simplicity and rapidity of the method recommended it over such alternatives as the oximeter, blood electrolyte studies and clinical observation. Since no adequate standards for resting minute volumes were available, standards were obtained (1) by a special formula, $M.V. = 0.292 \times Wt.^{0.75}$ (Kg.), relating this measurement to the body weight, and (2) by actual measurements on individual patients before ventilatory deficiency developed. Approximately eighty determinations were made on 5 patients with ventilatory deficiency, 4 with poliomyelitis and 1 with injury of the cervical portion of the spinal cord. The value of spirometry was demonstrated (1) in determining the proper respirator settings for effecting adequate ventilation, (2) in revealing day to day variations in ventilatory function, (3) in giving an objective indication or contraindication for placement in the respirator (4) in measuring ventilatory reserve and (5) in furnishing an objective criterion for removal from the respirator.

**Anoxia as a Cause of Fetal Death and Congenital Defect in the Mouse.** Dr. Theodore H. Ingalls, Dr. Francis J. Curley and Dr. Richard A. Prindle, Boston.

This paper was presented in full in the July 1950 issue of the American Journal of Diseases of Children, page 34.

**Renal Excretion of Phosphate in Newborn Infants: Observations in Normal Infants and in Infants with Hypocalcemic Tetany.** Dr. W. W. McCrory, Dr. C. W. Forman, Dr. H. McNamara and Dr. H. L. Barnett, New York.

Tetany of the newborn is a poorly defined clinical entity. The fact that a large group of such infants have hypocalcemia and elevated serum inorganic

phosphorus levels has led to the postulation of parathyroid insufficiency as a major factor in this condition. Although the relations between serum calcium and phosphorus is by no means simple, increase in serum inorganic phosphorus is usually accompanied by hypocalcemia. Since elevation of serum phosphorus would result from any limitation of renal excretion of phosphorus, the role of renal immaturity per se deserves critical study. The following data are directed toward evaluation of the relative importance of variations in degree of parathyroid function and renal immaturity in causing elevation of serum phosphorus.

Mechanisms involved in renal excretion of phosphorus were studied by observing the response of 6 normal infants to ingested phosphate (0.5 to 1.5 Gm. of sodium phosphate). The amount of phosphorus filtered increased as the serum level was elevated (13 to 14 mg. per hundred milliliter). Reabsorption remained essentially unchanged, and, consequently, excretion paralleled filtered load as it exceeded the rate of reabsorption.

The amount of phosphorus filtered, reabsorbed and excreted in 7 infants, with endogenous elevations of serum phosphorus (8.4 to 9.6 mg. per hundred milliliters), 4 of whom had clinical tetany, was compared with the findings in normal infants. Tubular reabsorption of phosphorus was not increased. The amount of filtered and excreted phosphorus was in the same range as that of infants with endogenous levels below 8 mg. per hundred milliliters. Since filtered phosphorus is the product of serum phosphorus and glomerular filtration rate, the latter must be reduced in these infants with endogenously elevated serum phosphorus levels. A measurable reduction in inulin clearance was found.

The complex question of the role of variations in parathyroid function in causing elevation of serum phosphorus was approached by observing the response of infants to parathyroid preparations. A prompt increase in renal excretion of phosphorus associated with decrease in reabsorption followed the injection of 15 units of a parathyroid preparation intravenously. The response of 4 infants with clinical tetany and 4 normal infants was identical. To determine the effect of phosphorus intake on renal excretion, the response of the same infant to ingested phosphate was observed after periods of high and low phosphorus intake. A marked increase in reabsorption and decrease in excretion was found after limitation of phosphorus intake with aluminum hydroxide for five days. If these changes can be interpreted as a decrease in endogenous parathyroid activity, this degree of hypofunction is associated with a measurable increase in reabsorption. Values for reabsorption in infants with endogenously elevated serum phosphorus levels did not approach these high values, but, as stated, were in the same range as those of infants with normal serum phosphorus levels.

In conclusion, our data indicate that elevation of endogenous serum phosphorus levels in newborn infants with or without tetany can be related to a reduction in glomerular filtration rate. We have no evidence supporting the hypothesis that infants with endogenously elevated serum phosphorus levels and tetany differ from normal infants in their degree of parathyroid function if variations in tubular reabsorption of phosphorus reflect such function.

**The Parathyroid Glands and Phosphorus Homeostasis.** Dr. J. D. Crawford, Dr. M. M. Osborne, Dr. N. B. Talbot and Dr. M. L. Terry, Boston.

This paper presents information concerning the manner in which parathyroid hormone controls renal phosphorus excretion and shows how this information can be used as an index of physiologic changes in parathyroid activity. These findings may be summarized thus:

1. In the absence of parathyroid hormone (after parathyroidectomy) the renal tubules reabsorb all the phosphorus filtered at the glomerulus. As parathyroid

hormone concentration is increased, as by administration of parathyroid extract, the tubules reabsorb a progressively smaller fraction of glomerular filtrate phosphorus. Maximum parathyroid effect results in complete inhibition of tubular phosphorus reabsorption, and all the glomerular filtrate phosphorus appears in the urine. Because no factor other than parathyroid hormone exerts a comparable effect, it is concluded that the ratio of tubular reabsorption of phosphorus (T.R.P.) to glomerular filtration of phosphorus (G.F.P.) may be used as an index of parathyroid activity at the renal tubule.

2. Application of the T.R.P./G.F.P. index suggests that the parathyroid glands normally undergo fluctuations in activity in order to accomplish homeostasis of serum phosphorus. The glands appear to be stimulated to increased activity not only by hypocalcemia but also by an elevation in serum phosphorus concentration. The response to hyperphospheremia occasioned by a sudden increase in phosphorus intake is evident within one to three hours. Complete parathyroid adaptation to such an increased phosphorus load may be accomplished within twelve to twenty-four hours. Completed adaptation is characterized by phosphorus balance and return of serum phosphorus concentration to the normal range.

3. The clinical applicability of these findings is illustrated by studies on newborn infants. Such studies show the homeostatic capacity of the parathyroid glands to be grossly limited during the neonatal period. Transient hypoparathyroidism accounts for the tendency of tetany to develop in newborn infants when they are fed formulas of high phosphorus content.

**Renal Functional Studies in Experimental and Clinical Dehydration in Early Infancy.** Dr. Philip L. Calcagno and Dr. Mitchell I. Rubin, Buffalo.

Alterations occurring in renal function during dehydration in infants with diarrhea and vomiting have not been defined clearly.

Young and McCance, studying 7 infants with diarrheal disease, concluded that there is no evidence that a specific renal lesion exists. However, from their published data we are unable to calculate the percentage change in glomerular filtration rate during diarrhea.

Black, McCance and Young induced water deprivation in 4 normal adult subjects, reducing their weight from 4 to 7 per cent. They found again that the glomerular filtration rate was not significantly diminished. Barnett and his associates, in a study of premature infants with "moderate" water deprivation, maintained that there was no significant diminution in glomerular filtration rate as measured by inulin clearance and that water conservation was accomplished by the mechanism of tubular reabsorption.

Our experiments were designed to determine the changes in renal mechanism brought about when dehydration induced by water deprivation was of the magnitude seen in clinical disease states and to compare the changes in the experimentally dehydrated infant to those of the infant with the clinical disease, with diarrhea and with vomiting.

The effects of dehydration in these three conditions were studied in 19 infants. Seven infants were deprived of water for four to five days, resulting in 3 to 10 per cent loss of body weight. Daily intake of water varied from 20 to 45 cc. per kilogram per day. Caloric intake was not altered from the usual amounts. Nine infants were admitted to Children's Hospital with diarrhea, and 4 were infants vomiting because of pyloric stenosis. The initial study of renal function was made shortly after admission, and subsequent observations were repeated within two weeks.

In infants with water deprivation whose caloric intake was not significantly reduced the glomerular filtration rate fell significantly (from 39 to 68 per cent of the nondehydrated state). These figures represent values uncorrected for surface and are average values for two or more periods in each child. In 4 infants with hypertrophic pyloric stenosis, the fall in glomerular filtration rate was comparable to that in the infants with water deprivation alone. Again, the changes in diarrheal disease (water and food deprivation) are similar to those of experimental water deprivation alone and of vomiting from pyloric stenosis. It is thus apparent that in severe dehydration, in contrast to the findings on infants during milder dehydration, reported by the authors mentioned, the glomerular filtration rate is significantly reduced and serves, along with tubular reabsorption, as a mechanism of water conservation.

The U/P (urea/plasma) ratio, a measurement of tubular water reabsorption (water conservation), in the experimentally dehydrated infant was elevated, as was to be expected, the highest figure being 306, the lowest 110. This was also true in children with pyloric stenosis. However, in the children dehydrated by diarrhea with equally depressed glomerular filtration rates, the U/P ratios were lower than was to be expected, suggesting a possible defective tubular mechanism. Selkurt found a similar decline in U/P ratio and maximal rate of paraaminohippuric acid reabsorption when tubular damage was induced by renal ischemia. During dehydration there was a greater fall in urea clearance than in the inulin or creatinine clearance.

Sodium and chlorine were conserved by the renal tubules in the three types of dehydration. The conservation occurred in experimental water deprivation in the face of plasma hyperosmolarity. Potassium losses in diarrheal states were relatively greater than in water deprivation alone. In the former condition tissue breakdown with starvation offers more potassium for excretion, in contrast to the latter condition in which tissue breakdown has not occurred. Similar losses occurred in pyloric stenosis. The urinary losses were much more apparent with fluid therapy. There was a rapid recovery of glomerular filtration rate with intravenous fluid therapy.

The conclusions of the experiments were these:

1. Dehydration when of sufficient severity depresses the glomerular filtration rate significantly. The greater fall of urea clearance over inulin and creatin clearance, especially in the diarrhea and pyloric cases, indicates that the fall in glomerular filtration rate may actually enhance water conservation by the tubules.

2. The lower than expected rise in U/P ratio with low urine flows during dehydration in diarrheal disease suggests a disturbed tubular mechanism for water reabsorption.

3. Electrolytes are also conserved by the mechanisms involved in water conservation.

4. Potassium is lost in greater amounts in those conditions in which tissue breakdown occurs to a greater extent than in water deprivation alone (starvation with diarrhea and vomiting).

5. The glomerular filtration rate is rapidly restored with intravenous fluid therapy. In the infants with severe dehydration from diarrheal disease restoration to normal values proceeded at a slower pace.

**Total Body Water in Children.** Dr. Bent J. Friis-Hansen, Dr. Malcolm Holliday and Dr. Thomas Stapleton, Boston.

Total body water was determined in 24 normal infants and children from birth to 11 years of age. The body water was determined simultaneously by

deuterium oxide dilution and by the antipyrine method. Micromodifications of both methods were used, which enabled the determinations to be made on capillary blood. The results obtained by the two methods agreed closely.

The body water expressed as per cent of body weight was found to be highest during the neonatal period, varying between 72 and 83 per cent of body weight; the values for 4 premature infants fell within the same range as those for full term infants. There was a decline in the total body water expressed as per cent of body weight during the first six months of life. From 6 months to 11 years of age it varied between 53 and 63 per cent.

The linear relation of body water to weight and surface area for the age group studied was described. The major factor influencing body water content was shown to be fat. The part played by changing composition of the body was discussed.

**Electrocardiographic Patterns in the Diagnosis of Operable Congenital Heart Diseases: Review of 105 Cases Proved by Operation or Autopsy.** Dr. Alexander S. Nadas, Dr. Lester G. Josephs, Dr. Mariano M. Alimurung and Dr. Benedict F. Massell, Boston.

Since the successful operative approach to a number of congenital cardiac abnormalities is a living reality today, an accurate diagnosis of a congenital heart lesion is of utmost importance. The findings of the physical examination and roentgenographic and fluoroscopic examinations have been repeatedly described. Electrocardiography is being discussed in most instances only in the vague and unimportant terms of axis deviations. On the basis of our experience, we believe the electrocardiograph, with unipolar chest and extremity leads, is a key instrument in the diagnosis of congenital heart disease. As a matter of fact, we have found it to be the most useful tool in determining ventricular hypertrophy.

Fifty cases of patent ductus arteriosus, 25 of tetralogy of Fallot, 25 of coarctation of the aorta and 5 of underdeveloped right ventricle with tricuspid atresia have been analyzed from the electrocardiographic viewpoint.

Characteristic patterns for each of these anomalies can be described. The presence of these changes should permit the cardiologist to refer his patient for surgical treatment without elaborate physiologic studies. Deviation from these patterns should suggest further investigation in terms of cardiac catheterization or angiography before operative intervention.

## Third Session

### *Tuesday Morning, May 9*

**Immunologic and Biochemical Studies on Infants and Children with Special Reference to Rheumatic Fever: IX. The Hematologic and Metabolic Effects of ACTH Administration.** Dr. H. Helper, Dr. R. Lubschez, Dr. K. Hain and Dr. M. G. Wilson, New York.

The sharp drop in onsets and recurrences of rheumatic fever after puberty suggests that hormonal factors may be involved in the pathogenesis of this disease.

This investigation is primarily concerned with the hematologic and metabolic effects of pituitary adrenocorticotropic hormone (ACTH) in doses of 50 to 100 mg. for four to seven twenty-four hour periods. A comparison of the observations on normal and genetically susceptible children and on patients with acute rheumatic fever is presented.

There was no significant difference in the hematologic and metabolic effects in the patients studied during administration of ACTH. In patients with acute

rheumatic fever the eosinophil count before treatment was below normal. The blood pressure was not significantly elevated during the administration of ACTH.

There was no significant effect in the serum electrolytes. There was a slight elevation of fasting blood sugar in all the groups studied.

The urinary excretion of sodium and chloride was markedly diminished in all the cases. The variation in potassium excretion remained within normal limits. There was a transient glycosuria in several patients. The excretion of 17-ketosteroids and 11-oxysteroids was increased during the administration of ACTH.

The significant effects during administration of ACTH were evidenced in the following order: (1) hematologic changes characterized by a fall in circulating eosinophils and lymphocytes and a concurrent rise in leukocytes and neutrophils, (2) drop in temperature to normal in twenty-four hours, (3) decreased chloride and sodium excretion associated with a rise in uric acid/creatinine ratio, (4) increased excretion of urinary steroids noted in all groups and (5) glycosuria of mild degree and slight rise in blood sugar.

The clinical response in 10 patients with acute rheumatic carditis to the administration of ACTH was characterized by a dramatic drop in temperature to within normal limits in twelve to twenty-four hours. Objective evidence of cessation of active carditis by the third day was evidenced by the general well-being of the child, disappearance of precordial distress and drop in respiratory and pulse rates. Auscultation revealed that new murmurs present for the first time had disappeared, while murmurs present before the attack had reappeared. The tenderness of the liver disappeared. Objective evidence of a progressive increase in cardiac reserve was demonstrated by a consistent increase in vital capacity. Of particular importance is the regression of enlargement of the chambers of the heart as demonstrated by fluoroscopic examination. The diminished cardiac size remained thus for three weeks to seven months. The associated symptoms of polyarthritis and erythema multiforme subsided within tweny-four to forty-eight hours.

In the 1 patient with chorea the gross movements disappeared by the third day.

In 2 patients the course of the acute rheumatic process was interrupted. In one use of ACTH was discontinued on the fourth day, and in the other the dose was reduced on the third day for experimental purposes. The clinical signs of active rheumatic fever which recurred were significantly less than before administration of ACTH. After a period of four to five days administration of ACTH was again followed by cessation of the acute rheumatic process.

In 10 patients with acute rheumatic carditis during administration of ACTH in a dose of 50 to 100 mg. for a period of four to seven twenty-four hour periods evidence was obtained to indicate that the acute rheumatic process appeared to be interrupted or terminated.

**The Response of the Hyaluronidase Inhibitor and Mucoproteins in ACTH Therapy of Rheumatic States.** Dr. Forrest H. Adams, Dr. Vincent C. Kelley, Dr. Paul F. Dwan and Dr. David Glick, Minneapolis.

In 1928 Duran-Reynals described the enhancing effect of testicular extracts on the invasion of a virus in the experimental animal. In 1930 McLean, working with the same substance, gave it the name "spreading factor." Chain and Duthie in 1939 and 1940 showed that the substances Duran-Reynals and McLean were studying were identical and that it was an enzyme, which they called hyaluronidase because it hydrolyzed hyaluronic acid. Numerous investigators since have demonstrated that hyaluronidase is found in many bacteria, snake venom, bee sting and leech head extracts. Since hyaluronidase contains protein, it is

antigenic; therefore, specific antibodies develop against the hyaluronidase injected from any specific source. It has also been demonstrated that there is, in addition to the specific antibody or inhibitor, a nonspecific inhibitor in the serum of practically all animals and in man. The latter inhibitor can affect the hyaluronidase from any source. This nonspecific inhibitor is not an antibody and has certain other physical characteristics that distinguish it from the specific antibody.

Serum mucoproteins are proteins in the serum that are rich in carbohydrate, hexosamine and sulfur and low in nitrogen content and found normally in animals and man. Winzler has described the determination and isolation of these substances and noted that in certain disease conditions these serum proteins become markedly elevated.

It has been demonstrated in our laboratories that the serum levels of the nonspecific hyaluronidase inhibitor and of the mucoproteins are elevated in acute rheumatic fever, rheumatoid arthritis and numerous other conditions and that the levels of these entities are regulated by an adrenal mechanism. It has also been demonstrated that the administration of pituitary adrenocorticotropic hormone (ACTH) to normal animals and to hypoglycemic human subjects causes elevation of these serum levels. In view of the demonstration of the effectiveness of adrenocorticotropic hormone therapy in the same diseases in which these values are elevated, it seemed of basic importance to attempt to elucidate further any relation that might exist. For this reason the present study of the response of the nonspecific hyaluronidase inhibitor and the mucoproteins to the administration of ACTH in patients acutely ill with rheumatic fever and rheumatoid arthritis was undertaken.

Eleven patients with acute rheumatic fever and 2 with juvenile rheumatoid arthritis were the subjects of this investigation. One of the patients with acute rheumatic fever also had diabetes mellitus which had been present previous to the onset of his rheumatic fever. The ages of the patients ranged from 4 to 16 years, and the sex distribution was approximately equal. After a control period of one to five days ACTH was administered intramuscularly in doses ranging from 40 to 100 mg. per day. The average duration of the treatment was approximately four weeks. Fasting blood specimens were obtained every day or every other day for the following determinations: hemoglobin, eosinophil count, sedimentation rate, nonspecific hyaluronidase inhibitor and mucoproteins. Serums were likewise saved at critical periods of the study for iontophoretic and total protein analysis. The following additional tests or studies of secondary interest were made: daily electrocardiograms, electroencephalograms, determinations of heart size and psychiatric evaluation.

The sedimentation rate and the hyaluronidase inhibitor level dropped rapidly during the administration of ACTH. This seemed to follow closely the subjective improvement in the patient's condition. Not only did the ACTH effect the quick drop in the hyaluronidase inhibitor level, but in all instances the level became subnormal, as has been observed in patients with inactive rheumatic fever. The serum mucoproteins, however, were much slower in their return toward the normal. This was in contrast to the observations in patients with acute rheumatic fever who had not received ACTH. Under such conditions the serum levels in the mucoproteins and the hyaluronidase inhibitor paralleled each other quite closely. In instances in which the ACTH was withdrawn or the dose was cut too low before a substantial drop of the mucoprotein level had taken place, the patient had a recurrence of the disease. This occurred even though the dose was not changed until the sedimentation rate and the hyaluronidase inhibitor level were normal. In general, the fasting eosinophil count increased during ACTH therapy

at the same time the nonspecific hyaluronidase inhibitor level, and the sedimentation rate fell to normal values.

ACTH administered to the patient with combined diabetes mellitus and rheumatic fever effected an increase in the insulin requirements to approximately double that of the pre-ACTH period. As the ACTH was gradually withdrawn, the insulin requirements returned to the previous amount.

Clinically the ACTH relieved the patients of their acute symptoms, as has been observed by others. It was felt that the natural duration of the disease was probably shortened and that the cardiac disability was kept to a minimum and was prevented from progressing.

The impression was gained that the mucoproteins are a better indication of the patient's rheumatic activity and that the hyaluronidase inhibitor and sedimentation rate are better indications of the adequacy of the ACTH dosage.

**The Effects of ACTH and Cortisone on the Nephrotic Syndrome.** Dr. Henry L. Barnett, Dr. Helen McNamara, Dr. Wallace McCrory and Carolyn Forman, New York, and Dr. Milton Rapoport, Dr. Alexander Michie and Dr. Giulio Barbero, Philadelphia.

Clinical, metabolic and physiologic observations on the effect of pituitary adrenocorticotropic hormone and cortisone in children with the nephrotic syndrome are presented. Our interest in examining the effect of these agents is directed toward an increased understanding of the disease. Although edema is not considered of basic importance in affecting the course of the disease, sustained remissions tend to follow spontaneous, rapid and profuse diureses. Induction of this type of diuresis may be followed by a remission whether or not the agent used is in itself related to the disease. Although their spontaneous occurrence makes evaluation of induced diuresis difficult, it seems clear that ACTH is capable of evoking such responses.

Typical water and sodium diureses resulting in loss of approximately one-third control weight occurred either during administration or after withdrawal of ACTH. Our present experience has been that doses of 50 to 100 mg. of ACTH a day for seven to ten days induced diuresis thirteen times in thirteen trials in 8 children. This and larger doses have failed to induce diuresis three times in 2 children. No responses were seen in children receiving equivalent or smaller doses for five days or less, although sufficient adrenal stimulation to lower eosinophil counts and increase fasting blood sugar was observed. No real diureses have been seen in 5 children given 100 mg. of cortisone a day for ten days. There was no difference in age, sex, duration of symptoms or degree of reduction of renal function between those who did and those who did not have diuresis.

Changes in serum sodium, potassium, chloride, bicarbonate, urea nitrogen and urinary protein during therapy and diureses were irregular and inconsistent. Milky serum cleared after administration of ACTH, and serum lipid fractionations consistently showed marked falls in concentrations of total lipid and of each fraction. The per cent of phospholipid to total lipid increased from 16 to the normal 30 per cent and the ratio of phospholipid to cholesterol from below to above 1 per cent. Ahrens and Kunkel have shown that clearness of serum depends on this high proportion of phospholipid.

The most significant changes have been unexpectedly large increases (up to 3 times) in glomerular filtration rate during diuresis. Significant increases in plasma volume accompanied increases in inulin clearances. Increases in para-aminohippuric acid clearances were less than those in inulin clearances; hence

filtration fractions increased. Twenty-four hour clearances of endogenous creatinine, interpreted only as indicating when changes in glomerular filtration rate occurred, demonstrated that the glomerular filtration rate increased during the first twenty-four hours of diuresis.

In summary, ACTH in doses of 50 to 100 mg. a day for seven to twelve days induced rapid and sustained diureses in children with the nephrotic syndrome. Edema usually recurred, but subsequent responses followed repeated courses of ACTH, and sustained remissions have been observed. Inulin clearances showed unexpectedly large increases (up to 3 times) during diureses, and the glomerular filtration rate, estimated from corrected twenty-four hour endogenous creatinine clearances, remained significantly above the control level even when reaccumulation of edema fluid occurred. These findings suggest that reduced renal function in a child with the nephrotic syndrome should not be considered irreversible and that ACTH may be the best available tool to induce diuresis.

**The Effect of Adrenocorticotrophic Hormone (ACTH) on Salt and Water Excretion in Children with the Nephrotic Syndrome.** Dr. Conrad M. Riley, New York.

Fourteen children with nephrotic edema not accompanied by evidence of severe renal damage have been treated with ACTH. The majority were 2 to 4 years of age and received 15 mg. intramuscularly every six hours for four to six days. In 5 of these the edema was completely cleared in close time relation to the treatment; 3 of the 5 were treated again because of a symptomatic relapse occurring immediately in 1 patient and after one to two months in the other 2; the first failed to respond to the second course of ACTH. Four patients had a definite diuresis, but the edemas were not completely cleared; 2 of these were treated again immediately, with a similar incomplete response. The 5 remaining patients showed no significant response, and 2 of these still showed no change after a second period of treatment.

When diuresis occurred it usually began four to seven days after the beginning of treatment. This meant that frequently it began after withdrawal of ACTH, but in several instances brisk diuresis occurred while the drug was still being administered.

In terms of electrolytes and water, the diuresis was similar to that seen from any cause. There was a slight increase in urine volume a day or two before the outpouring of salt. Sodium and chloride concentrations in the urine rose from control levels of less than 10 milliequivalents per liter to the level of 130 milliequivalents. The total chloride loss in relation to the total sodium loss was in the range expected from the calculated composition of interstitial fluid rather than in considerable excess, as reported by some. The potassium concentration in the urine fell, but the total output per day showed no consistent changes. Daily urinary protein quantities decreased regularly but fell to zero in only 1 instance.

Immediately after cessation of diuresis several patients were given sodium acetate by mouth in large quantities. The urine sodium promptly increased, and there was no gain in weight, suggesting that at that time the kidneys were capable of clearing an increased sodium load.

In patients who manifested no significant diuresis there were, nevertheless, changes in the urine similar qualitatively to those mentioned for real diuresis. The order of change was very different, the sodium output rising from almost zero to little more than 6 to 8 milliequivalents a day.

Changes in blood components included a fairly consistent rise in serum sodium and carbon dioxide and a drop in total cholesterol. Hematocrit readings frequently showed a decrease during diuresis, but this was not consistent.

The preliminary impression gained from our brief period of work with these patients is that the course of the 9 who showed some response has been subsequently more benign than expected in a similar number of random patients with nephrosis.

There were many striking inconsistencies which so far have defied explanation. No common factors were found among those patients who responded favorably to treatment and those who failed to respond. In both groups were patients who satisfied the criteria for the diagnosis of chronic nephritis as well as of "pure nephrosis." Antecedent duration of the disease also appeared not to be of significance.

Although ACTH does not invariably induce diuresis in nephrotic edema, it does so with enough regularity to prove itself a valuable tool in the study of the pathogenesis of the condition.

**The Treatment of Leukemia with ACTH and Cortisone.** DR. IRVING SCHULMAN, New York.

Since January 1950, 11 children with various types of leukemia have been treated with pituitary adrenocorticotropic hormone and cortisone. In this group were 10 boys and 1 girl, their ages ranging from 2 to 16 years. ACTH was administered in doses of 60 mg. a day in four divided doses for the first three days of therapy; this was followed by 40 mg. a day. Cortisone was administered in doses of 100 mg. a day, being increased in 2 resistant cases to 300 mg. a day. Four children were treated with ACTH alone, 4 with cortisone alone and 3 with combination of the two. The duration of therapy ranged from seven to seventy-one days. In this series were 6 children with acute lymphocytic leukemia, 1 each with acute granulocytic, acute monocytoid granulocytic and chronic granulocytic leukemia and 2 children with leukemic lymphoma.

Four children with acute lymphocytic and 1 with acute granulocytic leukemia exhibited a complete clinical and hematologic remission. One child with acute lymphocytic leukemia exhibited a slight temporary clinical and hematologic improvement. The others, namely, 1 patient with acute lymphocytic anemia and the patients with acute monocytoid granulocytic anemia, chronic granulocytic anemia and leukemic lymphoma exhibited no clinical or hematologic response whatever and died after seven to twenty-four days of therapy.

Of the 5 children who responded, only 1 had received previous therapy, "aminopterin" (4-aminopteroylglutamic acid) for ten months. Of the 6 children who failed to respond or responded minimally 5 had received previous treatment, 2 with "aminopterin," 2 with radiation, 1 with urethane U. S. P.

In those children who responded clinical improvement was rapid and dramatic. Striking improvement in appetite, activity and general well-being was evident during the first week of therapy. Bone pain present in 2 of the patients disappeared in two days after the onset of therapy. Purpuric manifestations in 1 patient also ceased in two days.

Hematologically the first signs of improvement were a sharp drop in the number of blasts and the appearance of mature white cells in the peripheral blood, this being evident within four to six days. The percentage of granulocytes rose rapidly, and the differential count became normal in two to four weeks. All 5 children who responded began with a leukopenia, with the total white cell count rising slowly but steadily and reaching normal values in three to four weeks.

A rise in thrombocyte (platelet) count was seen in four to eighteen days, and a maximum reticulocyte response occurred in the second or third week, after which the red cell count and hemoglobin rose steadily to normal values. In only 1 patient was transfusion required, and in this patient a reticulocytosis has already occurred.

In the marrow the first evidence of improvement was the appearance of increased numbers of erythrocytic elements. This was usually evident in one week. Maximum marrow improvement occurred in three to four weeks in every case. In 3 patients the blasts fell to levels below 3 per cent, and in the other 2 the blasts were 8 and 7 per cent at the time of maximal improvement. In 3 of the children who exhibited clinical and hematologic remission there occurred, however, within three to six weeks from the onset of therapy, evidence of hematologic relapse with reappearance of increasing numbers of blasts in the marrow. In 1 patient evidence of marrow reversion occurred within one week after completion of a three week course of ACTH therapy and progressed despite resumption of administration of ACTH at a higher dosage level for an additional three weeks. In a second patient marrow reversion occurred while the patient was still receiving ACTH and progressed despite a shift to cortisone therapy for three weeks. In 1 patient who had exhibited very rapid and complete remission an attempt was made to study the effect on the occurrence of relapse of the administration of small maintenance doses of ACTH in the amount of 10 mg. once a day. However, four weeks after the introduction of maintenance therapy there was evidence of hematologic relapse, with a rise in percentage of blasts in the marrow to 25 per cent, drop in thrombocytes and recurrence of an abnormal differential formula. In addition, eosinophils became evident in the marrow and peripheral blood to the extent of 10 per cent. A second course of ACTH, 60 mg. a day, was given. The platelets again rose, the differential formula became normal and the blasts again fell to 4 per cent. Throughout the fourteen week period following the initial course the child has been completely asymptomatic. One patient, on the other hand, remained in complete remission fifteen weeks after the onset of therapy; it is of interest that this child received the shortest course of therapy, ACTH for twelve days. The last patient, who has been followed for eight weeks after a three week course of cortisone, also shows no evidence of relapse at this time.

In summary, ACTH and cortisone have produced striking remission in 5 of 11 children with leukemia. In 3, however, hematologic relapse was evident early, 1 responding and 2 being resistant to second courses of therapy. Two of the children remained in complete remission fifteen and eight weeks, respectively, from the onset of therapy.

It is our impression that prolonged therapy has no value in preventing hematologic relapse or prolonging remission. In fact, this may preclude a second course of therapy at higher dosage levels because of the development of undesirable endocrine effects.

**Studies with 2, 2-Bis(Parachlorophenyl)-1,1-Dichlorethane, a New Adrenocorticolytic Agent.** Dr. John Nichols and Dr. Lytt I. Gardner, Chapel Hill, N. C.

The chemotherapy of malignant processes and hyperplasia depends on the development of chemical compounds which affect specific cell types. The response of breast and prostatic cancer to steroid therapy and the response of leukemia to the folic acid antagonists and cortisone are cases in point. The following studies have been made on the action of 2,2-bis(parachlorophenyl)-1,1-dichlorethane in producing atrophy of the adrenal cortex.

Mongrel dogs were fed 200 mg. a day of this compound dissolved in corn oil for periods ranging from two weeks to two months. Histologic examination of the adrenal glands revealed severe atrophy of the zona fasciculata and the zona reticularis with sparing of the glomeruli, in confirmation of the observations of previous workers. In none of the dogs did any clinical evidence of adrena cortical sodium-potassium hormone deficiency develop. Preliminary experiments indicate that such animals are sensitive to insulin, suggesting deficiency of adrenal oxycorticosteroids.

It is hoped that elucidation of toxicity thresholds and species specificity may permit the application of this compound in the treatment of adrenal cortical carcinoma and hyperplasia (including the pediatric syndrome of persistent hyperplasia of the androgenic zone). Extreme caution is urged in the use of this chemical.

**Absence of Tetany or Respiratory Change with Lowering of the Plasma Hydrogen Ion Concentration Experimentally Produced by Bicarbonate Administration.** Dr. C. D. West and Dr. S. Rapoport, Cincinnati.

It is commonly assumed by pediatricians that an increase of the plasma bicarbonate produced by the administration of alkalizing salts to normal persons is followed by a compensatory diminution in the rate of ventilation which tends to minimize changes in $p_H$. Also it is thought that elevation of $p_H$ produced by the administration of alkali may cause tetany. These assumptions are not supported either by studies in the literature or by the experiments to be reported.

Large quantities of sodium bicarbonate were injected intravenously into unanesthetized dogs. Although $p_H$ rose as high as 7.8, there was no change in respiration as indicated by the plasma carbon dioxide tension. Tetany failed to occur.

It appears that elevation of plasma $p_H$ has remarkably little effect on either respiration or neuromuscular irritability, in contrast to the marked stimulation of respiration and inhibition of tetany produced by lowering of $p_H$. Also, variations in plasma bicarbonate have little influence on respiration and neuromuscular irritability, while changes in carbon dioxide have profound effects.

**Lipemic Nephrosis in Rats: Description of the Disease and Studies on the Metabolism of the Nephrotic Kidney.** Dr. Walter Heymann, Cleveland.

Chronic renal disease was induced by the intravenous injection of antikidney serums obtained from rabbits into 235 rats of the Long-Evans strain. They were inoculated when 4 to 5 weeks old with seventy-eight different serums obtained from 33 different rabbits.

Massive proteinuria without gross hematuria was noted within a day or two. Microscopic hematuria was observed in 27 per cent of the rats at onset and in 6 per cent in late stages of the disease. Marked edema and ascites developed in 35 per cent during the first three to four weeks and recurred only rarely during late stages. Thirty-three per cent died within two weeks. In 14 per cent a chronic disease without remissions for as long as fifteen months developed. In 6 per cent the course was characterized by remissions and exacerbations. Spontaneous cures were noted as late as five to eight months after onset in 30 per cent. Seventy-four per cent remained normotensive, while 26 per cent showed moderate fluctuating hypertension. None died of uremia. Hypoproteinemia and hyperlipemia developed within eight to twelve hours, were marked and were regularly observed. An initial

azotemia, without creatine retention or hypertension, subsided within three to four weeks. In severely sick rats tubular lesions and fatty degeneration were seen early in 75 and 57 per cent respectively. Some interstitial nephritis was noted in 46 per cent as a late lesion. Diffuse glomerular lesions occurred early, and focal glomerular disease was noted late in 69 per cent of the animals. Thirty-one per cent were free of visible glomerular disease. The oxygen uptake of kidney slices was studied with the Warburg technic in 30 nephrotic rats. The inability of glucose in 0.02 molar concentration to increase the oxygen uptake normally seems to be a specific metabolic lesion. It was found to be present even when alanine, acetoacetate, butyrate, glutamate, succinate and lactate yielded normal results. Since the three latter substrates may be utilized normally, it is concluded that the Krebs tricarboxylic acid cycle is intact and that the lesion has to be looked for in the anaerobiotic phase of carbohydrate metabolism.

**The Nephrotic Syndrome in Children: A Physiologic Interpretation Based on Clearance Methods.** DR. JACK METCOFF, DR. WESTON KELSEY and DR. C. A. JANEWAY, Boston.

This report suggests that the clinical variants of the nephrotic syndrome in children may be interpreted physiologically as successive phases of a single diffuse renal disease.

Twenty-seven children, a representative sample of 85 patients with nephrosis observed from January 1949 to March 1950, have been studied by detailed renal clearance technics. Differential clinical criteria applied early in the nephrotic syndrome frequently proved unreliable indexes of specific renal functions or subsequent course of the patient.

The glomerular filtration rate (GFR), determined by inulin and/or thiosulfate clearance, was uniformly diminished during the initial two months. Occasionally "supernormal" glomerular filtration rate followed within six months. More commonly, progressive reduction occurred. Early reduction of glomerular filtration rate apparently did not preclude remission, nor did supernormal levels assure recovery.

Validity of renal plasma flow measurement (RPF) depends on virtually complete renal extraction of plasma paraaminohippuric acid per unit time. Ablation of functioning parenchyma decreases effective extraction and may invalidate estimation of clearance. Observed data on renal plasma flow may be corrected utilizing Cargill's approximation of extraction derived from arteriovenous paraaminohippuric acid differences. Corrected renal plasma flow data were variable early in the syndrome. Persistence of renal disease was associated with consistent, progressive reduction of renal plasma flow.

Decreasing renal plasma flow was correlated with disproportionately greater glomerular filtration rate reduction. The filtration fraction was usually reduced. Correction of renal flow for extraction amended spuriously high filtration fraction values frequently observed with extensive renal damage.

Maximal tubular excretion (Tm) of paraaminohippuric acid afforded an index of functioning tubular tissue. Correlation of the glomerular filtration rate and maximal tubular reabsorption revealed initially scattered values but relatively symmetric reduction of functioning nephrons with progressive disease.

Plasma flow per unit of functioning tubular parenchyma, denoted by the ratio RPF: Tm, suggested relatively increased flow to residual tubular tissue, perhaps characterizing vascular shunts. Occasional negative maximal tubular reabsorption values were observed.

Renal hemodynamic concepts postulate that effective tubule plasma flow is inversely proportional to filtrate extraction; their product, a constant defining a rectangular hyperbola. The observed distribution of nephrotic data suggested that progressing renal ischemia was associated with glomerular obliteration.

The validity of clearance measurements at very reduced levels of renal function is uncertain; their interpretation, hazardous. With this reservation further qualified by the necessity for protracted observation, these studies of the nephrotic syndrome suggest that the initial renal insult diffusely involves the entire nephron. Preponderance of glomerular or tubular malfunction may occur. Hypothetically, reduction of primary glomerular filtration rate and of filtration fraction might be associated with dilatation of the efferent glomerular arteriole and increased subcapsular pressure contingent on increased resistance of the glomerular membrane. Inadequate tubular reabsorption of protein might constitute a compensatory mechanism for reducing oncotic pressure. Homeostasis would be abetted by slight constriction of the efferent arteriole. Further constriction could induce "supernormal" glomerular filtration. Recovery would attend successful functional reorganization. Obliteration of glomeruli with progressive disease would demand vascular shunting. Relatively increased plasma flow adjacent to residual tubular tissue would represent spurious hyperemia and presage renal failure.

Since children, unlike adults, often recover from the nephrotic syndrome, adaptability and pattern of immunogenic response in the younger organism may be fundamental variables.

# Book Reviews

**Food and Facts for the Diabetic.** By Joseph H. Barach, M.D., F.A.C.P. Price, $4. Pp. 219, with 16 figures and 21 tables. Oxford University Press, 114 5th Ave., New York 11, 1949.

Dr. Barach's book is dedicated to the enlightenment of the diabetic patient, for, as he says, "it is our conviction to-day that many diabetics will outlive many nondiabetics, because they will have learned how to live according to the laws of health."

The book is divided into two parts. The first part deals with clinical manifestations of diabetes, laboratory diagnosis, planned diabetic treatment, principles of diet in health and disease, caloric value of foods, quantitative values in the measured diet, insulin, complications in the use of insulin, causes of high sugar levels in the blood and urine and their control, hygiene—a way of life for the diabetic, complications in diabetes, diabetic coma and its treatment, prevention of diabetes and its complications and diabetes in children. The material is presented in a simple and lucid style and is well supplemented with explanatory figures and helpful charts.

The reader is introduced to the nature of diabetes and its symptoms, the methods of collecting specimens of urine and the various tests in the routine care and management of the disease, general principles of dietary treatment and a discussion of the nature of foods and the part played by carbohydrates, proteins and fats, as well as minerals and vitamins, both in health and in diabetes. A chapter dealing with the calculation of the diet and the daily menu is enhanced by a valuable and easily calculable table of foods and exchange values in the substitution of everyday foods making up the daily menu. There follows a discussion of the rationale of insulin usage in diabetes, preparations used in administration of insulin, the nature of various insulins in current use and instructions to the patient. Insulin reaction is distinguished from diabetic coma in a precise outline and the means of overcoming insulin reaction are stressed; the diabetic patient is urged to keep on his body a standard identification card in case of emergency. In "A Way of Life for the Diabetic," the diabetic person is initiated into healthful living with rules of work and play; physical exertion and its effect on insulin dosage, adequate rest and sleep, the disadvantages of smoking and drinking and strict attention to personal hygiene in order to reduce the dangers of infections and the development of complications are also stressed. Equally important is the advice on complications in the diabetic person—what to do in case of a cold, the modifications in diet and insulin, the care of the feet and various exercises for the lower extremities. The factors for adequate growth and development of diabetic children and a guide to the use of adequate calories and insulin in the young diabetic patient complete this phase of the discussion.

The second part of the book contains a system of diets, tables of caloric values of foods, diets for men, women and children, emergency diets in case of illness and many helpful recipes. The diets are based on ideal weights for both adult and young persons and are also adjusted to meet the caloric requirements for the age, body height, body build and physical activity of the patient. This section is a valuable adjunct to the care of the diabetic person, as well as a convenient time-saver for the physician or nurse.

**Pediatrics and the Emotional Needs of the Child, As Discussed by Pediatricians and Psychiatrists at Hershey, Pennsylvania, March 6 to 8, 1947.** Edited by Helen L. Witmer. Price, $1.50. Pp. 180, with no illustrations. Commonwealth Fund, Division of Publications, 41 E. 57th St., New York 22, 1948.

In this book, 48 contributors of outstanding reputation discuss fully the emotional needs of the child as they see them from their respective fields—pediatrics, psychiatry, social service and nursing. Dr. Milton Senn, of New York, shows the need for longitudinal data in the study of emotions. Dr. A. H. Washburn, of Denver, presents several types of growth curves which seemed to show little or no effect from the environment and wonders whether or not the emotional reactions of a person may not depend as much on his characteristic temperament as on the provocations and frustrations of his environment. Dr. H. A. Murray, of Newark, N. J., emphasizes some of the mouth, anal and genital dynamics of growth and their significance in health and disease.

In Dr. B. M. Spock's opinion (N. Y.), the chief aim of pediatrics should be to avoid giving parents the kind of advice that inevitably creates difficulties between them and the child; especially, better guidance should be given during the second and third years. Mothers should use more natural methods with their children under 3 years of age—perhaps dare to spank a little instead of using too many warnings, moralizings and other gentle but subtly vicious measures. Dr. J. C. Montgomery, of Detroit, favors the rooming-in plan as making the mothers less afraid of their new babies. He also advocates use of the Gesell behavior day charts. Dr. J. L. Wilson, of Detroit, states that pediatrics has changed from a luxury to a necessity because the public is making an increasingly greater demand for pediatricians.

There is much discussion on the ways pediatricians can best be oriented psychiatrically. Miss Scoville brilliantly observes that the answer may not be found through special child psychiatric clinics but through a division of growth and development. Such a division will include the physical, emotional and social aspects. It will keep pediatric thinking focused on child development and preventive work and will not raise red flags between child psychiatrists and pediatricians concerning which specialist is to do the major psychotherapeutic work. In other words, many of the participants seem to say that "a stitch in time saves nine."

Finally, an appendix contains reports of ten teaching hospitals on their respective pediatric-psychiatric programs, but none seems adequate to meet the present teaching or therapeutic needs.

**Neurology.** By Roy R. Grinker, M.D., and Paul C. Bucy, M.D. Fourth edition. Price, $12.50. Pp. 1,138, with 515 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave, Springfield, Ill., 1949.

The fourth edition of this standard text has been rearranged and rewritten. While it has been revised by a neurosurgeon, the book retains its neurologic identity. The subject matter is clearly and simply written. It is illustrated by figures which can be readily understood. Throughout the book, careful attention has been given to neuroanatomy, neurophysiology and neuropathology, as a basis for the discussion of clinical neurology. A noteworthy feature of the book is the extensive reference to the literature. A large bibliography, alphabetically arranged, is included. This makes easy reference to monographs on pertinent subjects. The technic described for neurologic examinations, including roentgen ray and electroencephalographic procedures, will serve as a guide for the most careful clinical

investigation. The first part of the book is arranged anatomically, discussing the disorders of spinal roots and nerves, the brain stem and cranial nerves, the sympathetic nervous system, the cerebrum and the motor systems. Other chapters describe the clinical manifestations of inflammation, intoxication, degeneration and trauma. The developmental defects, the epilepsies, the myopathies and headaches are all adequately considered.

This book is somewhat massive for the undergraduate. It will adequately serve the postgraduate and the clinical neurologist. It should be found exceedingly valuable by clinicians in other fields. The clarity of its style, its easy reading, the authenticity of its subject matter and the extensive bibliography make it a superior reference volume for clinicians generally.

**Observations on Pathology of Hydrocephalus.** By Dorothy S. Russell. Price, 6 shillings. Pp. 138, with 90 figures. His Majesty's Stationery Office, York House, Kingsway, London, W.C.2, 1949.

Professor Russell's monograph takes as its thesis that all instances of hydrocephalus are caused by obstruction in the circulation of the cerebrospinal fluid. In a large series of cases studied personally by her, the cause of the obstruction was found in every instance. The material is presented on an etiologic basis, with carefully reasoned comments, illustrative case histories, exceptionally good photographs and reviews of relevant experimental data when available. The chapters deal successively with maldevelopments, gliosis of the aqueduct, inflammations, thrombosis of the dural sinuses and neoplasms. Then follows a section dealing with the anatomic effects of hydrocephalus per se on the central nervous system and its coverings. Of special interest is the excellent discussion on hydrocephalus following recovery from meningitis, particularly in view of recent success in the treatment of meningitis by antibiotics and sulfonamides. Russell also marshals convincing arguments that some instances of hydrocephalus previously regarded as "idiopathic" are sequelae of unrecognized attacks of meningitis months or years before hydrocephalus becomes clinically manifest. Evidence is presented that long survival after thrombosis of the dural sinuses may be accompanied with hydrocephalus which is perhaps reversible in part.

The monograph is written with utmost clarity and conciseness and in a style that makes its reading a pleasure. The paper and printing are good, as are the reproductions and illustrations. It is unfortunate that a volume which will be so often consulted should have a flimsy paper binding.

This book not only fills a long acknowledged need but also serves as an invaluable guide to all concerned with hydrocephalus either in the laboratory or in the clinic. To the pediatrician it is indispensable in dealing with hydrocephalic patients and in recognizing factors which may be antecedent to this condition. To the neuropathologist and neurosurgeon, it is a book to be read and reread, at once a reference, a guide and a stimulus to further work.

**Symposium on Newer Synthetic Analgesics.** By M. L. Tainter and others. Annals of the New York Academy of Sciences, volume 51, article 1. Price, $2.75. Pp. 174, with charts and graphs only. The New York Academy of Sciences, American Museum of Natural History, Central Park W. and 77th St., New York 24, 1948.

For those physicians who are particularly interested in the action of synthetic analgesic drugs, this publication by the New York Academy of Sciences is extremely appropriate. Since the relief of pain is one of the first duties of all

physicians, this review of the analgesic drugs should be readily available to each of them.

Among the new findings brought out by this symposium is the fact that meperidine (demerol®) hydrochloride is of no value in the treatment of biliary colic, since it has a decided constrictive effect on the sphincter of Oddi and will increase pain from the biliary tract by its spasmogenic action.

The new synthetic drug methadone hydrochloride has probably only a limited value as an analgesic and at present has its chief use in the oral treatment of pain in patients with cancer for whom its cheapness and effectiveness may cause it eventually to succeed metopon hydrochloride, an opium derivative which has recently been suggested for this specific purpose. Harris and Wikler, working at the Public Health Service hospital in Lexington, Ky., for the treatment of narcotic addicts, have reported that methadone is as addictive as morphine but that its longer duration of action tends to obscure its abstinence syndrome. Of some two hundred derivatives of methadone studied by Chen, none have properties superior to those of methadone itself.

This particular review also contains additional valuable data on the testing of the newer analgesic drugs in man and animal.

**Allergy in Relation to Otolaryngology.** By French K. Hansel, M.D. With a panel discussion by H. A. Abramson and others. Price, $2.50. Pp. 77, with 6 plates and 2 tables. Bruce Publishing Company, 2642 University Ave., St. Paul, Minn., 1949.

This small book is designated as an official publication of the American College of Allergists. It consists of three parts: The first bears the title of the work; the second is labeled "Panel Discussion," and the third "Questions and Answers Following Panel Discussion." Nowhere is the reader told where or when the panel discussion and question period took place.

The author deserves great credit as a pioneer in the field of otolaryngologic allergy. His observations are concisely stated; the technic of preparation of nasal smears is well outlined, and there is a well merited plea for conservatism in regard to adenotonsillectomy and surgical treatment of sinusitis. Emphasis is laid on cooperation between the otolaryngologist and the allergist and on the desirability of agreement concerning which procedures are necessary and best for the patient.

The panel discussion does not come off quite so well. This section contains much irrelevant circumlocution and too much unscientific therapeutic speculation, although one participant presents a fair summary of the psychosomatic aspects of the allergy problem. The question and answer portion is insignificant.

In short, this book may be read with profit by those who remember to stop at the end of the first section.

**For the New Mother.** By Mildred V. Hardcastle, R.N. Price, $2. Pp. 163, with illustrations. The John C. Winston Company, 1006-1016 Arch St., Philadelphia 7, 1949.

This is a good book in its field. The content is complete, simply written and calmly presented. So far as this reviewer can see the advice is sound, logical and modern in concept. No controversial material is presented, and no attempt is made to prescribe treatment. Simple directions are included for all routine procedures involved in the daily care of an infant up to 1 year of age. The subject of growth and development is simply, interestingly and sensibly presented.

Menu suggestions for quick meals for the family are included to save the mother from becoming overtired when first home. Advice is given on baby sitters, short trips with baby and many other things that can be a real problem to the new mother.

All in all, the book is a good one. It can be safely recommended.

**Handbook of Diseases of the Skin.** By Richard L. Sutton, M. D., and Richard L. Sutton Jr., M.D. Price, $12.50. Pp. 749, with 1,057 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1949.

This book, according to the preface, is designed to be "useful to medical students, practitioners, and specialists in dermatology." The authors have, it seems, succeeded admirably as regards usefulness to practitioners and medical students but, in the opinion of the reviewer, the book cannot supplant the larger and more comprehensive standard treatises on the subject written for use by the dermatologist. Furthermore, the general tone of the work indicates that the authors lack, in some degree, the humility which characterizes the writings of some other well known authorities in the field, and the nondermatologist might well receive a biased opinion concerning certain matters which are generally regarded as controversial and complex but which the authors tend to oversimplify.

However, the illustrations in the book are uniformly excellent, the word descriptions of the various cutaneous diseases adequate and the discussions of treatment practical and implemented by many prescriptions. The work is a useful desk reference for the office of the busy pediatric practitioner.

**Répercussions sur l'enfant des maladies infectieuses de la mère pendant la grossesse (toxoplasmose et embryopathic rubéoleuse en particulier): Étude clinique, encéphalographique et sérologique.** By F. Bamatter. Price, 7.50 Swiss francs. Pp. 60, with 24 figures and 5 tables. S. Karger, Holbeinstrasse 22, Basel, Switzerland; 215 Fourth Ave., New York 3, 1949.

This monograph, a supplement to *Annales pædiatrici*, briefly reviews the effects of various maternal infections on the fetus, with particular attention to toxoplasmosis and rubella. The author adds several cases of his own, but no new information concerning the two infections mentioned. The bibliography, like the review, includes most of the important references but is far from comprehensive and omits certain reports in the American literature which have an important bearing on this subject.

**The Value of Hormones in General Practice.** By William N. Kemp, M.D. Price, $3. Pp. 115. Burgess Publishing Company, 426-428 S. 6th St., Minneapolis 15, 1949.

The author treats a large subject matter in a brief text. His expressed purpose is to assist general practitioners in the use of the many hormonal products now available. The physiologic background of each gland is discussed, followed by an outline of disease processes and treatments.

On the whole the author has done a good job. Of necessity, his discussion is brief and, therefore, somewhat dogmatic. In some cases the criticism might be made that endocrinology at present cannot be treated so briefly. Especially, one might object that administration of thiourea has not been proved to be entirely adequate in treatment of hyperthyroidism. Too little emphasis is laid on contraindications and hazards.

**Bananas: Chemistry, Physiology, Technology.** By Harry W. Von Loesecke. Price, $4.50. Pp. 201, with 51 tables and 29 figures. Interscience Publishers, Inc., 215 4th Ave., New York 3, 1949.

This book is concerned apparently with all phases of cultivation and handling of bananas, though the author states that it is intended for those engaged in fundamental researches. Emphasis is placed on the biochemistry of the fruit and its products. The book appears to be of greatest use to the agriculturist. It is of no medical interest.

**Your Child's Mind and Body: A Practical Guide for Parents.** By Helen Flanders Dunbar, M.D. Price, $2.95. Pp. 324. Random House, Inc., 457 Madison Ave., New York 22, 1949.

This book by one of the nation's authorities on psychosomatic medicine is intended to be a practical guide for parents in the rearing of their children. It is divided into nine chapters covering such subjects as sleeping, eating, playing, parental love, obedience, illness due to emotional conflicts, minor and major crimes and the child as a parent.

The approach is quite different from that of most books on child care. Throughout, the psychiatric point of view is stressed. How conflicts resulting from parental mistakes lead to excessive illness, accident proneness and emotional instability in adolescent and adult life is explained in the text and by case illustrations.

"Diarrhoea and vomiting may suggest that the individual is trying to rid himself of feelings of guilt."

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"Back of all superficial reasons for hay-fever is 'inner crying.'"

Parents who read this book may feel that the pathway which leads to emotional health and stability for their children is indeed a narrow one. Nevertheless, much sound advice is contained in its pages, and it is probably desirable that a book of this sort, stressing the relationship between mind and body, should be available not only for parents but for physicians as well.

**Manual of Medical Emergencies.** By Stuart C. Cullen, M.D., and E. G. Gross, M.D. Price, $3.75. Pp. 267, with 29 illustrations. The Year Book Publishers, Inc., 304 S. Dearborn St., Chicago 4, 1949.

This small volume contains the essential facts needed to manage emergency situations. The material presented is brief and to the point and contains no more information than would be expected of a manual. Only accepted principles of treatment are stressed, and it is unlikely that anyone could criticize the authors for the therapeutic suggestions presented. It does seem unwise to the reviewer, however, to attempt to present the management of conditions such as coronary thrombosis, surgical shock or cardiac arrhythmias in a manual of this type, since the treatment of such entities cannot be adequately discussed in only a few short pages.

# News and Comment

## ANNOUNCEMENTS

**Meeting on Child Safety, Sponsored by American Academy of Pediatrics and National Safety Council.**—The American Academy of Pediatrics and the National Safety Council will hold a joint meeting on Tuesday, October 17, at 8 p.m., in the Grand Ballroom of the Palmer House, Chicago, to discuss methods of preventing accidents among children. The main objectives of this joint meeting are (1) to focus national attention on the importance of child safety, (2) to develop practical methods whereby the medical profession and other safety interests can mutually aid in reducing the high accident toll among children and (3) to stimulate research in the cause and prevention of child accidents.

With the conquest of the communicable diseases of children, accidents now represent the leading cause of death and an outstanding cause of disablement and other injuries among children at all ages from 1 to 14. The highest rates are in the preschool and runabout age. Most of these accidents occur in and around the home. In an average year, accidents result in the death of more than 5,000 preschool children between the ages of 1 and 4. This is greater than the number of deaths from diphtheria which occurred annually in this age group nearly a quarter of a century ago, when this dread disease was considered an outstanding cause of child deaths. Concerted action leading to a reduction of accident mortality and morbidity among children is of timely importance.

The following program is planned for this joint meeting:

**Accidents: Childhood's Greatest Health Hazard**

| | |
|---|---|
| Presiding as Co-Chairmen: | Edward B. Shaw, M.D.<br>President of the American Academy of Pediatrics<br>Ned H. Dearborn<br>President of the National Safety Council |
| Organizing for Prevention | President of the National Safety Council |
| The Pediatric Approach to Accident Control | |
| (*a*) Through practice | Harry F. Dietrich, M.D., Los Angeles |
| (*b*) Through research | Rustin McIntosh, M.D., New York |
| The Challenge of Child Accident Prevention | Herold C. Hunt, Ph.D.<br>Superintendent of Schools, Chicago, Ill. |

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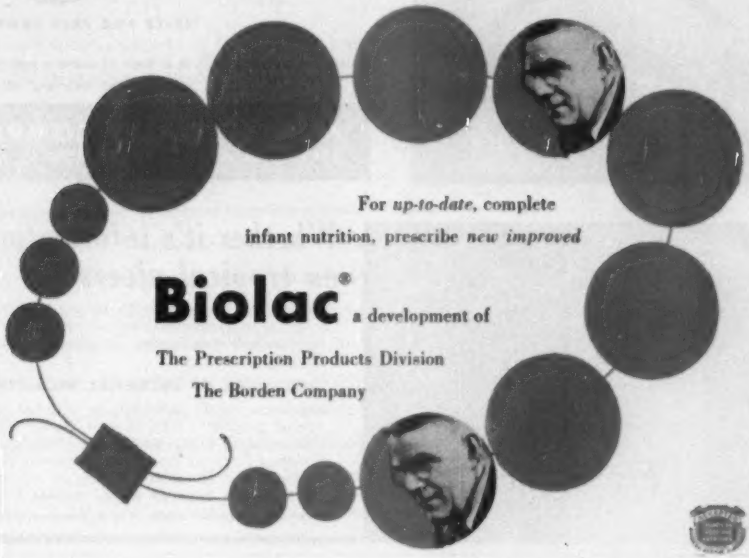


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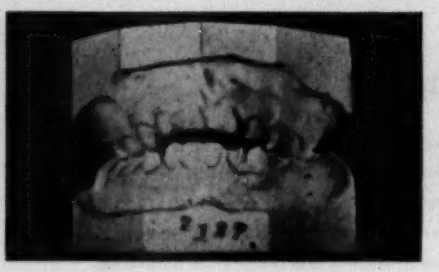

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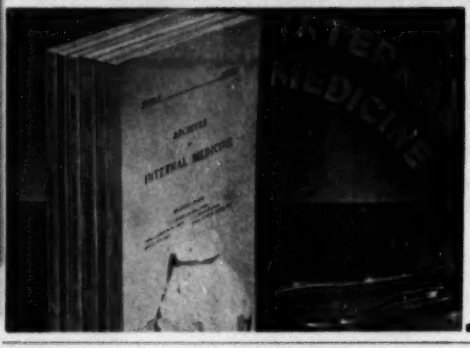


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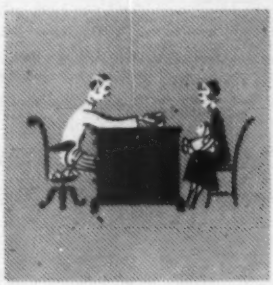

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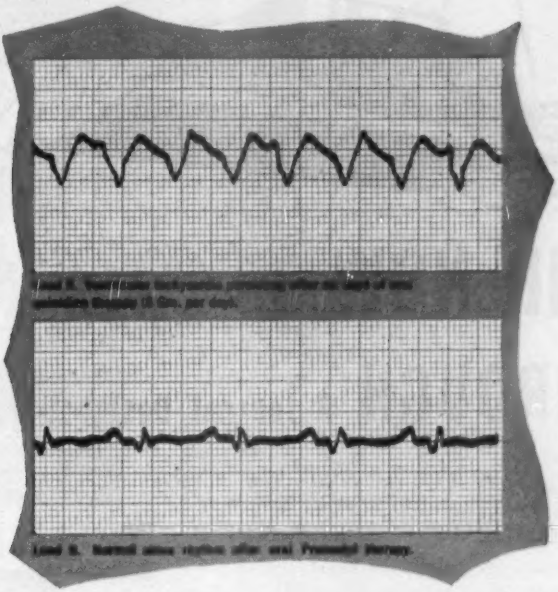

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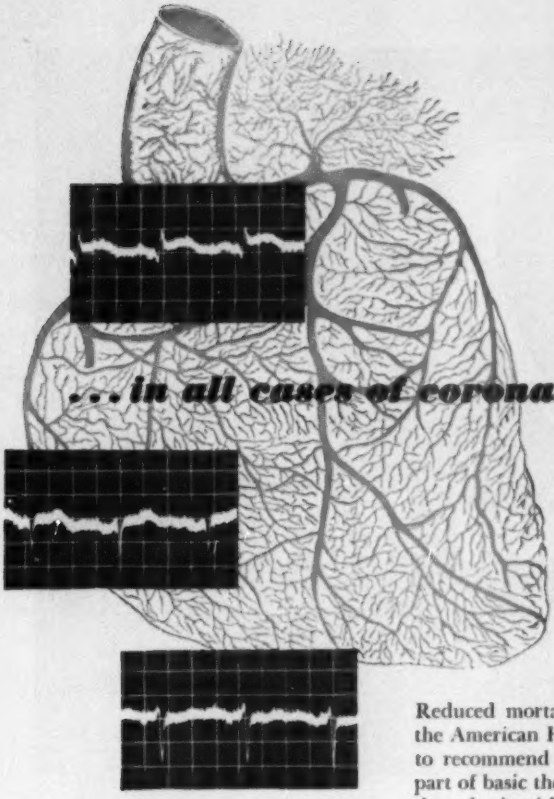

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1. *Wright, et al: Am. Heart J. 26, 801 (Dec.) 1943.*

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